VOL. 36 OCTOBER 1960 NO. 10

BULLETIN

OF THE NEW YORK ACADEMY OF MEDICINE

Original Articles by

HENRY S. KAPLAN

VICTOR H. WITTEN

IAGO GALDSTON

GLOMERULONEPHRITIS AND PYELONEPHRITIS

Transcription of a Panel Meeting

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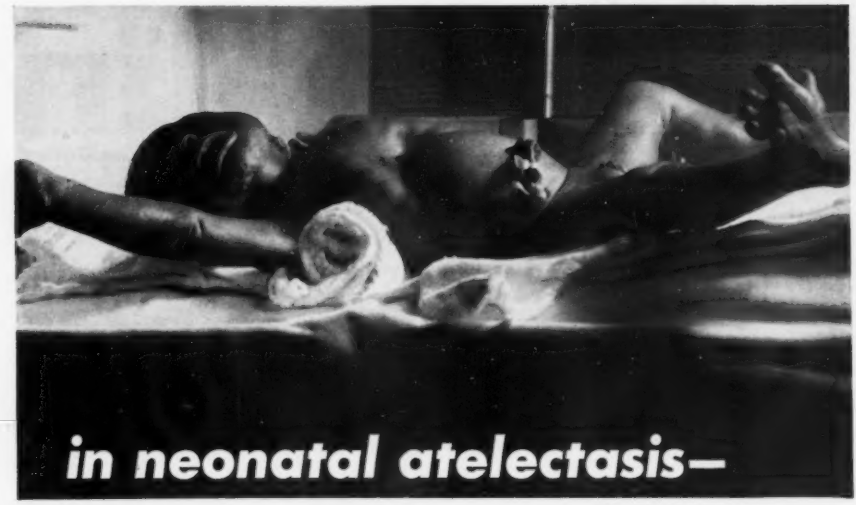

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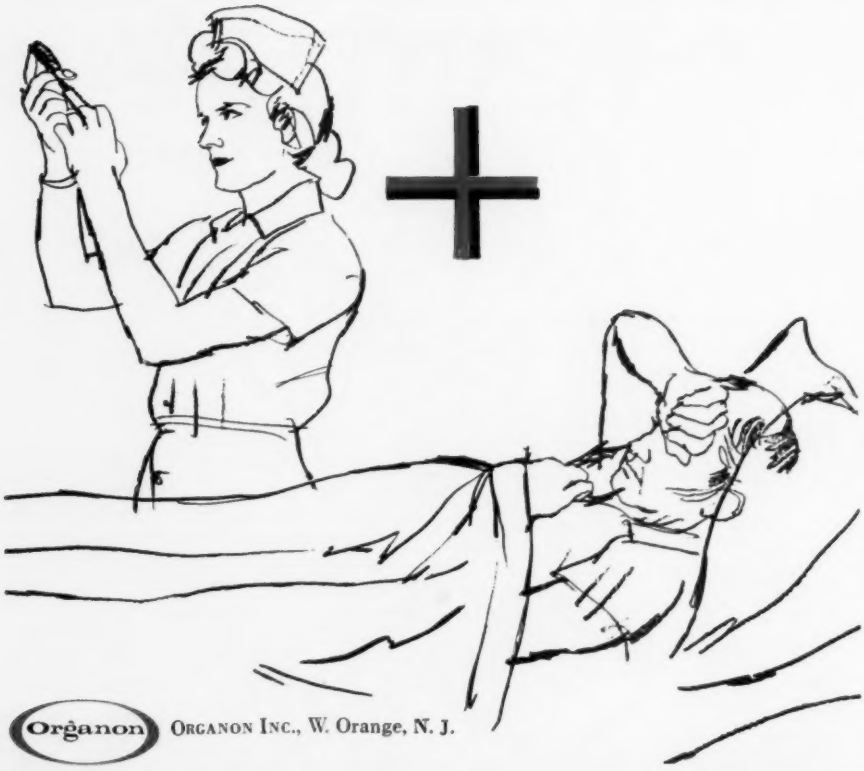

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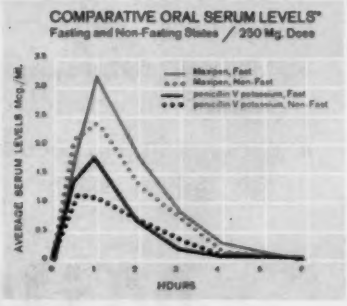

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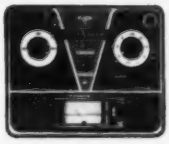
Simple, straightforward  operation

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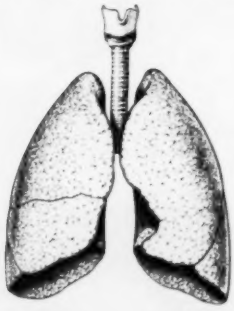

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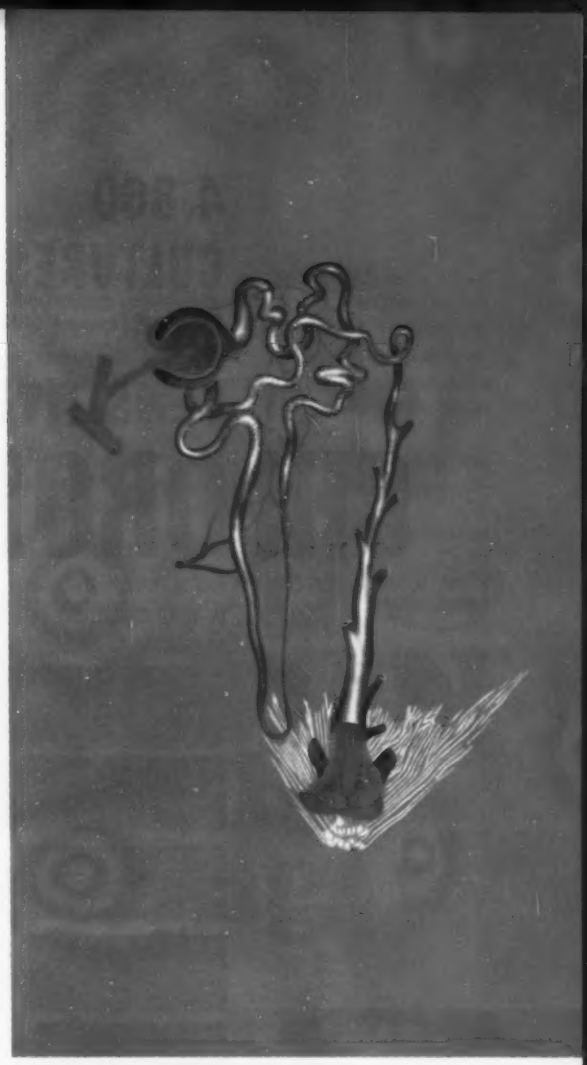

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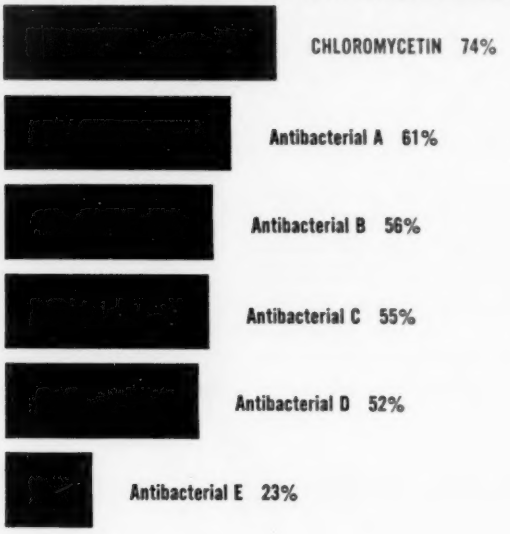

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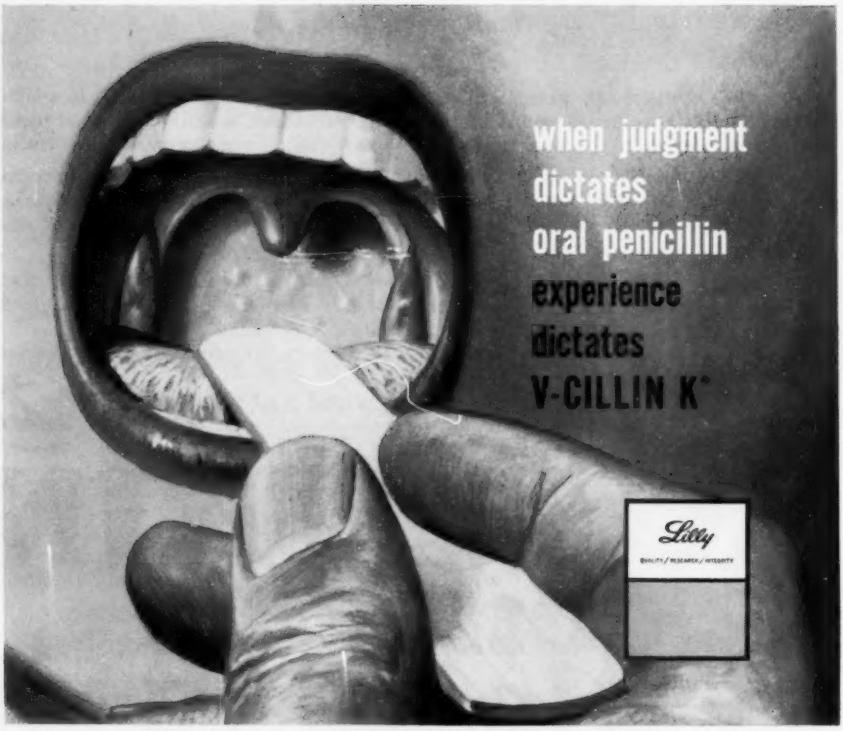

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1. Griffith, R. S.: Comparison of Antibiotic Activity in Sera Following the Administration of Three Different Penicillins, Antibiotic Med. & Clin. Therapy, 7:No. 2 (February), 1960.

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AUTHORS ALONE ARE RESPONSIBLE FOR OPINIONS EXPRESSED IN THEIR CONTRIBUTIONS

ROBERT L. CRAIG, *Editor*

Published Monthly by THE NEW YORK ACADEMY OF MEDICINE
2 East 103 Street, New York 29, N. Y.

Annual subscription United States and Canada $8.00. All other countries $9.00. Single copies 90c.
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BULLETIN OF
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VOL. 36, NO. 10 OCTOBER 1960

CELLULAR EFFECTS OF IONIZING RADIATION*

The Seventh Harlow Brooks Memorial Lecture

HENRY S. KAPLAN

Professor and Chairman, Department of Radiology, Stanford University School of Medicine
Stanford, California

IT is indeed a privilege to share with you this annual occasion which honors the memory of a distinguished New York physician, Dr. Harlow Brooks. I should like to speak tonight about some recent advances in the field of radiobiology, and the contributions which such studies may ultimately make through enhancing the efficacy of radiotherapy for malignant disease.

Radiotherapy and surgery are the only modalities which currently offer a significant chance of permanent cure for a variety of types of malignant disease. Both suffer from certain limitations, which have led physicians to hope that the newer field of chemotherapy would provide a more universal solution to the cancer problem. After some ten years of intensive research in chemotherapy, however, the inherent difficulties and limitations which also confront this approach have become in-

* Delivered at the Third Annual Postgraduate Week, *Research Contributions to Clinical Practice*, of The New York Academy of Medicine, October 7, 1959.

creasingly apparent. It is perhaps fitting then that we take a new look at the potentialities of radiotherapy.

The major limitations of radiotherapy are: (a) inadequate responsiveness of certain types of tumors; (b) instances of excessive injury to normal tissues; and (c) remote metastasis. The problem of tumor autonomy and metastasis is a vast and complex subject in its own right and we cannot hope to deal with it this evening. Although we must, for the present, admit defeat in the face of disseminated cancer, there is room for a great deal of improvement in the results of treatment for cancers which are still regionally localized. Even in the hands of the most experienced and capable radiotherapists, there is an appreciable frequency of recurrence at the primary site or in the regional lymph nodes. It is in this area that experimental radiobiology may aid in elucidating the underlying causes of radiotherapeutic failures.

We must start by examining the historical antecedents which underlie present radiotherapeutic practice[1]. As early as 1906, the French workers Bergonié and Tribondeau[2] announced a "law" of cellular radiosensitivity which, though based on scanty experimental evidence, still appears to hold up surprisingly well, with certain minor exceptions. They stated that the most radiosensitive cells were those which a) exhibited the highest mitotic rate, b) were destined to retain the capacity for division over the longest time, and c) exhibited the least differentiation.

The concept that different classes of cells have different radiosensitivities also received strong empirical support from the fact that some tumors may be cured without significant permanent damage to the surrounding tissues, from which the inference has seemed clear that the cells of the tumor must be more sensitive than the normal cells of the host. Experimental and clinical observations have yielded hierarchies of differential radiosensitivities for different classes of tumor cells and their normal counterparts, and these have been widely accepted in radiotherapy for some 40 years. Yet, as we shall see, both the significance and the very existence of differential radiosensitivity have been called into serious question by contemporary workers.

The early radiobiologic investigations of Regaud and his associates[3] revealed that fractionated doses of radiation, unlike single massive doses, could produce permanent inhibition of spermatogenesis in rabbit testes without concomitant injury to the scrotal skin. This classic work pro-

vided a foundation for the clinical trial of fractionated roentgen therapy by Coutard[4]. Coutard's methods resulted in a dramatic improvement in cure rates for cancer of the larynx and certain other primary sites in the head and neck, but great controversy soon raged as to which of the many points in his new technique deserved major credit for the improved end results. Today all radiotherapists accept fractionation as one of the cardinal tenets of good technique for all but the smallest, most superficial tumors, and would be reluctant to depart from the fractionation schedules with which they have become familiar.

The early studies of MacComb and Quimby[5] on the effect of two-dose fractionation on the erythema reaction in human skin indicated that recovery of normal skin might be more rapid than that of irradiated squamous carcinoma cells. During a repeated series of exposures, the normal skin would be expected to recover slightly faster after each dose, and might better withstand the next dose than the cancer cells. It is this concept which has constituted the major rationale for the long fractionated schedules which are the current expression of the Coutard technique. Through trial and error, fractionated doses which produce permanent regression of primary tumors with reasonably satisfactory regularity were established; for example, in the treatment of squamous cell cancers, doses of about 6,000 rads delivered in approximately five to six weeks of daily treatment are widely accepted as being proper tumoricidal doses.

So much for the historical background—let us now examine in some detail the essential features of cellular radiation injury. The killing of cells by ionizing radiation is a fascinating process which involves a complex chain of amplified reactions, starting with a very minuscule physical input of energy, which within microseconds may trigger a variety of free radical-mediated chemical disturbances in the aqueous medium and in certain of the macromolecular constituents of the cell. These chemical disturbances may then elicit a primary radiobiologic lesion. The subsequent expression of this lesion is a function of time and of mitotic activity, and is subject to modification by repair processes, including the usual nonspecific biologic reactions to injury. Since excellent reference sources for the physical and radiochemical aspects of the subject are readily available[6], I have chosen to concentrate on the biological and biochemical phases of the process, selecting material with particular relevance to clinical radiotherapy. The subject has also recently been

covered by Upton in a more comprehensive review[7].

Death of an irradiated cell is a relatively slow process, which may require several weeks. During this period, there is little or no apparent effect on the various synthetic, secretory, and other functional activities of the cell, with the sole exception of mitotic division. The cell seems able to do everything but divide, and looks normal enough except for its enormous size, which is the consequence of sustained synthesis of protein and other cell constituents, divorced from the usual partition of these products of growth among a succession of daughter cells[8]. Although we do not yet understand the essential nature of radiation injury to the mechanisms that regulate cell division, we know that unless repair has occurred by the time the mitotic process is finally triggered, the cell comes to grief during an abortive attempt at one of a succession of divisions. In a very real sense, then, the attempt by an irradiated cell to enter mitosis represents a form of suicide. Cells which are not called upon to divide because they have reached a post-mitotic level of differentiation (classical examples are nerve and muscle cells) are "immune" to radiation doses which are highly lethal for actively dividing cells. This is simply a restatement of the old "law" of Bergonié and Tribondeau, but with an important shift in emphasis.

Although it is essential, in the experimental study of this phenomenon, to artificially isolate certain facets (e.g., the morphological, the genetic, the biochemical, the physiologic), it is equally essential to comprehend the composite process through a resynthesis of all of its components, with particular attention to the coordination of time scales. Serial biopsy studies at intervals after radiation have long revealed a series of degenerative changes in the irradiated cells, but have suffered from the usual limitations of tissue morphology with respect to discontinuous sampling; thus the fate of individual cells could not be ascertained. Even more misleading information stemmed from early attempts to trace the biochemical pathway of radiation injury by measurement of changes in nucleic acid concentration or enzymatic activity in whole tissues comprised of mixtures of highly sensitive and resistant classes of cells. Since the most prominent manifestation of cellular radiation injury is that sustained by the reproductive apparatus of the cell, it is essential to employ experimental techniques which can reveal the fate of each individual cell in a population.

In his classical book[9], Lea developed arguments for a target theory

of cell inactivation. This theory postulates that the damage responsible for inactivation is sustained in a small "target" region of the cell, rather than diffusely throughout its volume, and that inactivation may result from a single ionizing event or "hit" within this target. For single hit effects, such as the inactivation of viruses, Lea showed that experimental data fulfilled several important predictions. There was a linear relationship between dose and the logarithm of the surviving fraction of virus particles, with the curve passing through the origin of the coordinates. Inactivation was independent of dose rate, as predicted, and radiations characterized by relatively sparse ionization, such as x or gamma rays and electrons, were more efficient than more intensely ionizing radiations such as alpha rays. Lea defined the inactivation dose, or D_{37}, as the dose which would permit survival of the fraction $\frac{1}{e}$, or 37 per cent of the initial population. The D_{10}, which permits survival of 10 per cent of the initial population, is obtained from the D_{37} by a simple conversion factor, and is more convenient to use with log scales of base 10. Lea predicted that cells containing a large number of unit targets, and vulnerable to inactivation by a "hit" in any one of these targets, should exhibit a correspondingly greater probability of inactivation and thus a correspondingly smaller D_{37}. Although Lea's target theory has undergone certain modifications[10] to take account of events occurring in the water molecules of the cell, these modifications have in essence increased the effective volume of the "target" without discrediting the basic theory. It was recognized that certain kinds of radiation effects, such as the production of chromosome breaks, might involve two or more adjacent targets, and would thus require two or more virtually simultaneous hits ("two-hit" inactivation). Atwood and Norman[11] calculated that in these instances the dose response curve would exhibit a shoulder near its origin, and would become essentially linear after a dose of perhaps two or three times the D_{37}, with the linear portion extrapolating to some integral number greater than one.

It must be admitted that most radiotherapists have not been impressed with the implications for clinical radiotherapy of Lea's work on virus inactivation and target theory. Recently, however, Puck and his associates, in a brilliant series of investigations[12, 13], have extended this work to mammalian cells cultivated *in vitro* under conditions in which the reproductive potential of each individual cell can be directly established after exposure to radiation. They found that human squamous

carcinoma cells apparently respond with a two-hit type of inactivation curve, and that the logarithmic fraction of surviving cells became essentially linear with increasing dose beyond the initial shoulder of the curve. Moreover, the D_{37} was only about 100 rads, in contrast to a D_{37} of about 10^5 rads for virus inactivation, suggesting that the much more sensitive mammalian cell may have correspondingly more unit targets, each independently vulnerable to inactivation.

The precision with which *in vitro* estimates of the D_{37} (or D_{10}) may be made for a variety of tumor cell types suggests the possibility of predicting tumoricidal doses on the basis of test responses in biopsied, cultured material. The considerations are, in certain respects, remarkably like those which entered into the production of the Salk poliomyelitis vaccine. We start by making reasonable estimates of the total numbers of tumor cells in the mass presented by the tumor. For example, an average squamous cell carcinoma having a volume of 1 cubic cm. would contain something like 10^9 tumor cells, if we neglect the stromal and vascular supporting elements. Let us assume a D_{10} *in vitro* of 200 rads. Doubling this dose would reduce the fraction of survivors from 10^{-1} to 10^{-2}, or one per cent of the initial population, and so on. We would then expect that a dose of 2400 rads (12 times the D_{10}) should leave a surviving fraction of 10^{-12}. Since the initial population was estimated at 10^9, this means that there would be less than one chance in 1000 that a single cell would still be left alive. Puck has applied this approach in the case of a squamous cell carcinoma (Hela) *in vitro*, and obtained an estimate for the single-exposure tumoricidal dose which is in quite good agreement with clinical experience for this type of neoplasm, encouraging the hope that the extrapolation from *in vitro* test to *in vivo* therapy may prove generally valid. The method should also lend itself to tumoricidal dose estimation for a variety of fractionated dose techniques. Such calculations also explain the paradox that tumoricidal doses for relatively large tumors and for very small tumors are not, in our clinical experience, very different. Thus, a tumor with a volume of 1,000 cubic cm. would, discounting its stromal and vascular content, contain a thousand times the number of cells in our initial 1 cubic cm. tumor, or roughly 10^{12} cells, and would require 3,000 rads (15 times the D_{10}), to afford the same probability of killing all cells. The difference in tumoricidal dose is only about 600 rads, despite the vast difference in size of the two initial tumors.

An important virtue of this quantitative approach is that it stresses the narrow margin of safety with which the radiotherapist must work. It is not enough to kill 99.9 per cent of 10 billion tumor cells, since the remaining 0.1 per cent, though a small fraction, would still represent about a million viable tumor cells. Since a very small difference in dose can make the difference between killing every last cell and leaving a few alive, techniques which increase the precision with which we may estimate tumoricidal levels would represent a most important advance.

Other studies by Puck provide a new challenge to one of our most long-cherished notions, namely, that of differential sensitivity of tumor and normal cells. Estimates of the D_{37} obtained by Puck for a variety of normal and neoplastic cells *in vitro* have been in startlingly close agreement with one another. However, this may reflect artificially high mitotic rates and lack of growth restraints for the normal cells in the extracorporeal environment. Valid measures of radiosensitivity *in vivo* are urgently needed to settle this issue. The work of Hewitt and Wilson[14] on the estimation of tumoricidal doses for leukemia cells is an ingenious extension of the Puck technique to *in vivo* conditions. Scott[15] has summarized the results of radiobiological studies with transplantable tumors; the possibility of distortion of responses through the action of subtle immunological differences between transplant and host represents a significant pitfall of such experimental work. In recent unpublished studies, my colleague, Dr. Robert F. Kallman, has demonstrated the practicability of using autochthonous (spontaneous or induced) animal tumors for radiotherapeutic investigations; preliminary data have been gratifyingly clean, and give promise of providing information of considerably greater reliability and significance to the radiotherapist.

If indeed it were true, as Puck suggests, that normal and tumor cells have about the same radiosensitivity, how would it be possible to destroy tumors while leaving the normal tissues viable? For certain types of cancers, notably the squamous cell carcinomas of the skin, lip, and oral mucosa, the small margin of therapeutic safety has long been clinically apparent. In these cases, this view is perhaps not so paradoxical as it seems, since many of the structural elements of connective tissue, such as collagen or matrix of bone and cartilage, retain their integrity long after the cells which secreted them have been destroyed. Thus the connective tissues around a cancer might be expected to maintain their

supporting function seemingly uninjured. However, the advent of trauma in a previously irradiated field would reveal the inability of the tissue to cope with a new functional demand for cellular proliferation. Other elements of the connective tissues are readily derived by differentiation from free-wandering stromal cells which may enter the injured field from remote, unirradiated parts of the body. Epithelium also apparently regenerates through the centripetal migration of cells from the unirradiated margins. It is therefore entirely conceivable that we may destroy both the normal and squamous tumor cells with almost equal efficiency, and yet that the end result may be a restoration of integrity of the normal tissues. However, certain types of tumors, such as the lymphomas and seminomas, respond clinically to much smaller doses, and must continue to be regarded as appreciably more radiosensitive. Nonetheless, the question raised by Puck is useful in providing a fresh re-emphasis of the long-standing radiotherapeutic precept that the volume of normal tissue subjected to heavy irradiation should be as small as possible, consistent with leaving a safe margin around the tumor, since volume considerations become of great importance in determining the probability that the normal tissues will be able to restore themselves to a viable state after regression of the tumor.

Is the essential injury nuclear or cytoplasmic? This important question has been reinvestigated in recent years with the aid of microbeams of heavy particle and ultraviolet radiation. Such studies[16,17] indicate that localized bombardment of the cytoplasm with tremendous doses elicits little or no effect, whereas bombardment of the nucleus, particularly over the chromosomes, is extremely effective after very small doses. It would thus appear that the major effect is within the nucleus, and that localized bombardment of the chromosomes has a very high probability of leading to abnormal and frequently fatal mitotic divisions. Bender[18] has observed the frequent occurrence of chromosome breaks in mammalian cells *in vitro* after doses as low as 50 r, and Read[10] has suggested that all lethal effects of radiation in the ordinary therapeutic dose range may stem from chromosomal injury.

Can the damage to chromosomes be repaired? The answer here is clearly "yes". The elegant studies of Wolff and his associates[19] indicate that repair is an energy-dependent metabolic process which is influenced by the availability of ATP and oxygen, and may be profoundly inhibited by protein synthesis inhibitors such as chloramphenicol.

Much effort has also gone into studies of the biochemical pathway by which the initial radiation injury is propagated. Many investigators have found an impairment of synthesis of deoxyribonucleic acid (DNA). However, as in the familiar chicken-and-egg problem, does the irradiated cell fail to divide because it is unable to make DNA, or does it fail to make DNA because it is unable to divide? The preponderance of current evidence supports the view that the decreased incorporation of labelled precursors into DNA following radiation is a secondary consequence of mitotic inhibition rather than a primary event[8]. The recent work of Kornberg[20] on the enzymatic synthesis of DNA *in vitro* indicates that pre-existing DNA (more specifically, a single-strand intermediate derived from the normal long double helical chain of DNA) must serve as the template on which the polymerizing enzyme builds new DNA molecules. Alexander and his associates[21] have stressed the importance of crosslinking in DNA irradiated *in vitro*. If crosslinking occurred between the two strands of a double helical chain, or between strands of adjacent helices, it would interfere with the uncoiling of the double helix to provide single-strand templates. After doses in the usual therapeutic range, only a small fraction of the DNA molecules in any one cell would have been affected, but the uniqueness of DNA molecules makes inactivation of even these few vitally important to the reproductive potential of the cell. Thus, the fact that over-all synthesis of DNA apparently continues at a level only slightly less than normal does not exclude the possibility that injury to a few specific DNA molecules, perhaps by crosslinking, might be the principal biochemical pathway through which radiation kills cells.

Can the response of cells to a given dose of radiation be modified by chemical means? It is known that the concentration of dissolved oxygen within the cell at the moment of irradiation can influence its response by a factor of about three. The effect is instantaneous, and pertains to the relative efficiencies of the various radiochemical disturbances triggered by the radiation, but the precise radiochemical locus of the oxygen effect is still open to debate[22]. The curve relating oxygen concentration to radiosensitivity is extremely steep at very low levels of oxygen concentration, but flattens out to a plateau at about 40 mm. Hg. oxygen pressure. Gray and his associates[23, 24] have pointed out that many tumors tend to outgrow their blood supply and that foci of anoxia and necrosis are prone to occur within them. Going back to our earlier

example of the 1 cubic cm. tumor containing 10^9 cells, let us assume that 0.1 per cent or 10^6 cells are highly anoxic and thus about three times as radioresistant. Another look at our dose response curve would indicate that the same dose of 2400 rads is only four times the estimated D_{10} of 600 r for the anoxic cells, leaving on the average something like one hundred of the anoxic cells unkilled. If, as a consequence of tumor shrinkage and the ingrowth of new stromal elements, these cells were to be provided with a new blood supply, they could resume growth and the tumor would thus recur. Gray points out that this may be a major source of primary failure in radiation therapy. Moreover, it has been suggested that the real virtue of Coutard fractionation may reside in the progressive ingrowth of vascular elements as the outer layers of the tumor regress, thus rendering initially hypoxic tumor cells vulnerable to later increments of radiation dose.

The delivery of more oxygen into the anoxic zones of tumors proves extremely difficult to do in practice, primarily because stasis of blood in these areas tends to shunt oxygen elsewhere. Churchill-Davidson and his associates[25] in England have attempted to increase the oxygen levels in anoxic zones of tumors by putting anesthetized patients into pressure tanks in which they are subjected to three atmospheres of oxygen during irradiation. Some of the initial observations on these very far advanced cases have been highly encouraging, but the method is so cumbersome as to make careful evaluation of large numbers of cases extremely difficult.

It may seem paradoxical, but it is the elimination of *differences* in oxygenation between the tumor cells and the normal tissues that is really important, rather than any arbitrary level of oxygen in either the normal or tumor cells. Another English investigator, Eric Wright[26], has suggested that it would be far easier to induce anoxia or hypoxia throughout a tumor than to build up oxygen levels in the zones that have been deprived of adequate blood supply. The total dose delivered to the tumor would have to be increased by nearly three fold, but inhomogeneities of response could theoretically thus be eliminated. Although complete anoxia would be too dangerous, the effect of tolerable levels of hypoxia is now being subjected to intensive experimental study in our laboratory, since the induction of hypoxia offers obvious practical advantages over the high pressure oxygen approach.

It has been known for several years that certain classes of compounds,

if present immediately preceding irradiation, can confer protection on cells, seemingly by reducing the effective dose of radiation delivered. Most of these have been sulfhydryl compounds, such as cysteine, glutathione, and beta-mercapto-ethylamine[27]. Earlier studies with transplantable animal tumors indicated that the protection conferred by these compounds on tumor cells and normal cells was essentially equal[28]. For this reason, and also because of their relatively high toxicity, these agents have not yet been subjected to extensive clinical trial in radiotherapy. However, there have been some indications of differential concentration of these compounds in different tissues[29], and there is renewed interest in the possibility that such compounds could, under appropriate conditions, differentially protect the normal tissues while allowing full expression of radiation damage in tumor cells.

Finally, increasing attention has been given in recent years to a search for other chemical sensitizers and potentiating agents which might enhance the response of cells to a given dose of radiation. Although early attempts along this line gave variable results[30], the work of Reese and associates[31] with triethylenemelamine and x-rays for retinoblastoma, and of Farber and co-workers[32] with a combination of Actinomycin-D and radiation for Wilms' tumor and other neoplasms in children have been distinctly more encouraging. More recent trials in our own department and at the University of Wisconsin with the new pyrimidine analog, 5-fluoro-uracil, in combination with radiotherapy have also been intriguing. My colleague, Dr. Malcolm Bagshaw[33] and others[34, 35] have used the Puck cell culture method as a screening system for the detection of such effects of combined therapy *in vitro*. A key question in such studies is that of differential effectiveness, since the same increase in therapeutic effect for both normal and tumor tissues would not really represent much of an improvement in the basic situation. Whether such differential enhancement of radiosensitivity can be attained or not remains to be determined, and will necessarily involve *in vivo* trials, both in animals and in man. Theoretical support for this eventuality is provided by the work of Heidelberger and his associates[36], who observed that tumor cells tend to concentrate 5-fluoro-uracil, relative to the normal tissues of the host. Although their initial uptake of the drug is perhaps no more efficient than that of the normal tissues, the tumor cells are apparently less able to eliminate it. Even a slight differential concentration of such a drug in a tumor might be considerably amplified

as a consequence of the interaction of its effects on early stages of DNA synthesis with those of irradiation. Intensive work along these lines seems amply justified by the prospect of two major clinical rewards: a decreased primary failure rate of radiotherapy in the treatment of those cancers in which it has traditionally been employed, and the possible extension of radiotherapy to those classes of tumors which have hitherto been considered radioresistant.

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GLOMERULONEPHRITIS AND PYELONEPHRITIS

*Transcription of a Panel Meeting**

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* Presented at the Second Annual Postgraduate Week at The New York Academy of Medicine, October 15, 1958.

MODERATOR WILLIAM GOLDRING: *I shall open the discussion by asking Dr. Merrill to present his views on the present status of the specific streptococcal types in the etiology of acute glomerulonephritis.*

DR. JOHN P. MERRILL: There is good evidence, although it is derived from a small series of cases, that several types of streptococci, designated as nephritogenic strains, would appear to be responsible for inducing acute glomerulonephritis following acute upper respiratory infection with Type IV, particularly Type XII and Type XXV of the Group A Lancefield streptococcus. Recently, in Great Britain, Type I has also been implicated. The fact that acute glomerulonephritis, unlike rheumatic fever, does not have a constant attack rate following streptococcal epidemics also suggests that this may be the case. I refer to epidemics of nephritis in which it has been specifically shown that this disease frequently followed infections with the streptococcal types mentioned. There are, of course, epidemics of nephritis which are non-strep in origin. Bates has reported some of these from the Great Lakes Naval Training Station.

Pneumococci and E. coli can also produce this syndrome. But, while certain types of strep predispose to glomerulonephritis, it is not invariably present when there is upper respiratory infection with streptococci.

One other point should be borne in mind: there is the possibility that the chronic or latent types of glomerulonephritis, which are not explosive in origin, may also be due to types of streptococci other than the so-called nephritogenic types, but may be responsible for the production of antikidney antibodies.

MODERATOR GOLDRING: *It is understood that any member of the panel, in disagreement with what is said, will speak up and give his views.*

DR. CONRAD M. RILEY: I should like to ask Dr. Merrill whether he thinks that this proposed etiology of nephritis has something to do with the fact that a second attack is almost never seen in a person who has recovered from a known attack of acute nephritis?

DR. MERRILL: That is what I meant. I hope we shall dwell on it a little later on. The fact is, we seldom see recurrences after the so-called explosive type of acute glomerulonephritis. In animals, this type has been fairly well correlated with the development of antikidney antibody, which has been demonstrated in the conventional immunological way. However, the kind of nephritis which is not preceded by an overt attack of pharyngitis, in which no obvious sudden acute attack

occurs, may also be caused by a streptococcus. In this instance, although no classic immunological bodies are developed, there may be such antibodies. Evidence for this exists in the case of a pair of identical twins in whom glomerulonephritis developed in a transplanted kidney even though there were no demonstrable antibodies of any sort. This leads me to believe that there may be two kinds of streptococcus-induced nephritis, and the first kind, because it does develop antibodies, may very seldom be followed by a second attack.

DR. GEORGE E. SCHREINER: Is it established that acute glomerulonephritis cannot be contracted twice? I think this prejudice is so deeply ingrained in clinical teaching that when we see a possible case it is almost subconsciously labeled an acute exacerbation. We assume something must have been going on in between.

We have one patient, age five, who was in Dr. Janeway's original series, with acute explosive glomerulonephritis, and who progressed to the nephrotic syndrome. This cleared and she was symptom-free with normal urines, on frequent checks, for five years. Her renal function tests also returned to normal. At the end of five years she reentered the hospital with hematuria, blood casts in the urine and oliguria. Had there been no history of a previous attack in this child, a diagnosis of acute glomerulonephritis would undoubtedly have been made. Because of the history, and with our prejudice so strong, we assumed something had been going on during the five year interval. We cannot establish that anything was going on, nor do we have, nor to my knowledge does anyone have, any series showing histological evidence of activity during these long periods of remission.

DR. MERRILL: Actually, Dr. Schreiner, this is what used to be referred to as focal nephritis. A case of this sort, documented by renal biopsy, was reported by Dr. McNeill of our group. This case had completely negative urines between attacks. The lesion was thought to be different from the acute proliferative type of nephritis. Perhaps it is different, at least slightly different, in pathology.

MODERATOR GOLDRING: Since we cannot resolve all questions today, we might continue and come back to that, if necessary.

Dr. Chasis, it is said that acute nephritis rarely, if ever, progresses to the chronic stage. What is your opinion?

DR. HERBERT CHASIS: We believe it does. A partial answer to this question has been given by Dr. Merrill and Dr. Schreiner, that is, that

it depends upon the diagnostic criteria used. We think that acute nephritis and chronic nephritis are phases of one disease, with many variations and manifestations in its course.

As you know, there are two schools of thought on this question. There are those who believe that acute nephritis and chronic nephritis are separate entities. They base their argument on the fact that in many chronic nephritics there is no history of preexisting disease; that, in children particularly, progress from acute to chronic disease is rarely observed; that pathological findings differ; and finally, that there is an absence of anti-streptococcal antibodies in the circulating blood of chronic nephritics. All these objections can be answered but, rather than discuss theoretical aspects of this problem, I should like to present a series of biopsies on one patient which we think demonstrates progress from the acute to the chronic stage of glomerulonephritis.

Four renal biopsies were done on a 46 year old male, the first during the second week of his illness, the second during the second month, the third during the fourth month, and the fourth during the sixth month. This work is being carried on at New York University College of Medicine in the Departments of Pathology and Medicine by Drs. Robert McCluskey and David Baldwin.

(Slide) This patient had typical acute hemorrhagic glomerulonephritis, with hematuria, proteinuria, azotemia, edema and hypertension. The first slide (H and E stain), reveals the typical findings of acute nephritis, as manifested by hypercellularity and polymorphonuclear infiltration; the basement membrane is normal, as shown in the next slide stained by the azocarmine technique.

The second biopsy, taken two months later, reveals subsiding glomerulonephritis, with less infiltration and less hypercellularity, but still shows a normal-appearing basement membrane.

(Slide) Four months later the acute changes have subsided. Thickening of the basement membrane, however, is beginning and can be seen in this section stained by the PAS technique.

(Slide) Six months later the basement membrane is thick and irregular and all inflammatory signs have disappeared. Clinically, the patient had subsidence of acute manifestations by the third month and by the sixth month was readmitted with what might be called the nephrotic syndrome, in that he had proteinuria and edema. Had the patient been seen for the first time in the sixth month, without the

story of the acute episode, one would have thought he had the nephrotic syndrome and that the pathological changes observed at the time of the biopsy were consistent with chronic glomerulonephritis.

Evidence such as this tends to confirm our clinical impression that acute nephritis progresses to the chronic stage of nephritis in about 16 per cent of patients.

DR. SCHREINER: We would tend to agree with Dr. Chasis. We have at least ten patients who, under observation, have progressed from the acute to the chronic stage of post-streptococcal glomerulonephritis. Evidence for the origin was in the form of positive cultures for streptococcus and elevated streptolysin titers. Under direct observation they have progressed without any break into a chronic phase and have died in uremia. We had one child who did all this in a period just short of 24 months. The biopsy was done at three and one half years of age. This child had glomerulonephritis at six months, the nephrotic syndrome at one year and died at a little over four years of age with the classical chronic glomerulonephritis with hyalinized glomeruli. I cannot see how there can be any doubt that, in some patients at least, the disease can progress through all the stages within a short span. The difficulty is that, in other patients, the span may extend from 30 to 40 years. A single individual physician rarely gets the chance to observe the natural history of the sequential progress of the disease process within his professional lifetime.

MODERATOR GOLDRING: *Not so long ago the opposite view was held by many, particularly the pediatricians, that acute nephritis is a disease entirely different in its pathogenesis from chronic nephritis. Ellis has a classification that points to this by designating Types I and II. Now, with the longer periods of observation and with more thought given to the problem, it is apparent, at least to some, that acute and chronic nephritis can be phases of one and the same disease.*

DR. SCHREINER: (Slide) This is the biopsy from a 19 year old boy in West Virginia who had a severe streptococcal pharyngitis, who was admitted to our hospital with oliguria, with blood casts in his urine, and who subsequently became anuric and was dialyzed, a procedure that we shall discuss a little later. Here you see that, in the short space of approximately three weeks, there is a glomerulus with marked fibrinoid necrosis in its center. This is a glomerulus with marked epithelial cell proliferation, beginning crescent and massive fibrinoid necrosis in

the center, a good explanation of why he was anuric, showing that changes can progress in remarkably short periods of time.

DR. RILEY: Dr. Chasis, when you use the figure, "16 per cent of patients with acute glomerulonephritis," are you referring to all ages or only to adults?

DR. CHASIS: That figure was derived from 150 patients with acute diffuse glomerulonephritis seen on both the pediatric and adult services at Bellevue Hospital. There were more adults than children in the series. The 16 per cent figure is probably high since not all nephritics enter a hospital for the acute stage, while in others there may be so few symptoms or manifestations that the diagnosis is not made. How these patients would influence the statistics is not known.

MODERATOR GOLDRING: *Dr. Schreiner, do you recognize so-called nephrosis as a renal disease different from glomerulonephritis? What is your definition?*

DR. SCHREINER: We believe that the term "nephrotic syndrome" is a clinical condition and have recently proposed a more elastic definition than the classical one commonly given in textbooks. In our opinion, this is a condition that begins with a change in the capillary basement membrane. It is characterized by excessive protein loss and the finding of double refractile lipid bodies in the urine, with attendant hyperlipemia, albuminemia and edema. This condition should obviously not be equated with glomerulonephritis. The clinician who approaches a patient exhibiting the nephrotic syndrome for the first time has the choice of a wide variety of etiologies, including glomerulonephritis, disseminated lupus, other types of collagen disease, Kimmelstiel-Wilson, typical or atypical amyloidosis, heavy metal poisoning, sickle cell anemia, interstitial nephritis, and renal vein thrombosis. In addition, a multiple number of sensitivity states have been described, such as poison oak sensitivity and post-immunization reactions.

We have been particularly interested in identifying sickle cell anemia, which had not hitherto been described as a cause of the nephrotic syndrome, and we have now studied three patients with this combination of events; one was a young boy and the other two were in a more elderly group of sickle cell patients. We have also recently encountered a patient with a condition of special interest. This patient appears to have a somewhat unusual type of membranal glomerulonephritis. We are not sure whether the histology is sufficiently unique

to call it descriptive, but in this case there is a type of membranal glomerulonephritis, with focal changes in scattered tubular cells and a full-fledged nephrotic syndrome after this patient had used ammoniated mercury ointment for two years. Another patient, who ingested daily oral doses of Neohydrin for a similar period, presented the same picture. We also understand that Dr. Becker, with whom I am corresponding, has a similar case in an elderly person here in New York, in whom the nephrotic syndrome, with no other etiology, followed administration of ammoniated mercury. So, we would then define nephrotic syndrome as a condition rather than a disease, with a nonspecific change in the glomerulus that may be brought about by any of a number of types of identified lesions.

(Slide) This shows a break-down in our series of 45 tissue-proven cases, in terms of the etiology that was determined. Thirty-nine of them were biopsied and six were autopsy cases, and the percentage of these patients with various diseases was as follows: 22 per cent had pure membrane glomerulonephritis, 47 per cent typical proliferative glomerulonephritis (?post-streptococcal). There were 7 per cent each of Kimmelstiel-Wilson, amyloidosis, disseminated lupus and sickle cell anemia. One patient, with interstitial nephritis following a staphylococcal enteritis, did have membranous changes in the glomeruli. The only patient in the series who had completely normal glomeruli was the patient who was recovering from bilateral renal vein thrombosis.

MODERATOR GOLDRING: *You did not use the term "nephrosis" but "nephrotic syndrome." Dr. Riley, what is your answer to the question put to Dr. Schreiner?*

DR. RILEY: I give a pediatrician's view on this. I think it is somewhat different from the internist's approach.

(Slide) I should like to point out that this is strictly a clinical grouping rather than one based on morphological studies. I would postulate two separate and easily recognized disease entities: acute glomerulonephritis on the one hand, and primary nephrotic syndrome on the other, which is what we deal with mostly in children. It is not always easy to distinguish a primary from a secondary nephrotic syndrome, a problem which frequently confronts the practitioner caring for adults. As I have indicated, the secondary type can arise, as Dr. Schreiner said, in association with lupus, Kimmelstiel-Wilson, drugs and all the rest of the names which I have lumped under "et cetera". The slide

indicates the possible progressions: that some idiopathic renal disease, anaphylactic purpura, or a familial trait may lead to chronic glomerulonephritis. The arrows without question-marks indicate usual routes. Where I have placed a question-mark, I wish to imply a rare pathway. Again, I am basing this grouping on my own experience, which has been limited to children. What I wind up with is a large waste basket in the middle of chronic glomerulonephritis, the origin of which I have never been sure, from a clinical point of view. Perhaps with the increasing use of renal biopsy we may remove some of the question-marks from this. But I am left with the thought that two definite entities, acute glomerulonephritis and the nephrotic syndrome as such, are recognizable. Primary nephrotic syndrome—I use this term for those caring for adults who don't like the word "nephrosis"—is a disease entity seen most often in children, though probably not infrequently in adults also.

MODERATOR GOLDRING: Dr. Chasis and Dr. Merrill, you can get into this, if you like. *Dr. Riley believes the term "nephrosis" should be continued. It has a meaning. I suppose he means etiologically and pathogenetically, as distinguished from other renal diseases associated with the nephrotic syndrome.*

DR. MERRILL: I should like to ask Dr. Riley two questions. He has already indicated that in acute glomerulonephritis in children, the tendency is probably greater towards complete healing than if there were nephrosis, as he terms it, with a phase of acute glomerulonephritis. May this not be the same disease in which complete healing of the nephrotic syndrome occurred so that a basement lesion was never seen?

Secondly, as I remember, it was Dr. Ehrich who, some years ago, restained many of the Rockefeller Institute sections of so-called pure lipoid nephrosis and found a very significant number of basement membrane glomerular lesions. In other words, is there not the possibility that our tools at the present are not sharp enough to pick up the basement membrane lesion in children?

DR. RILEY: This is a very real possibility. Some of the recent findings reported with electron microscopy tend to substantiate what you say. So, from the microsopic or ultramicrosopic point of view, in the nephrotic syndrome of unknown or idiopathic type there is undoubtedly a lesion of the basement membrane undetectable by the light microscope. I think Piel's work and Vernier's work make it likely that a lesion can always be found if suitable tools are used. This is a quite different lesion,

obviously, from the lesion in acute nephritis.

DR. SCHREINER: I prefer the term "syndrome" rather than any word which implies a distinct disease. If a woman of 45 years can become nephrotic by rubbing a mercurial ointment on an area of the skin affected by vitiligo, then who knows what happens when children are exposed to the many things which can produce a secondary syndrome?

MODERATOR GOLDRING: *Dr. Chasis, do you have a comment?*

DR. CHASIS: The term "nephrotic syndrome" should now be dropped. We used it as a stop-gap during the moratorium declared by the internist and the pediatrician in order to save valuable time in ways other than fruitless discussion. We really never believed there was an entity called "nephrotic syndrome". Now that the list has grown to include as many as ten or more diseases, and Dr. Schreiner has added sickle cell anemia as another disease in which the nephrotic syndrome occurs, it may be time to drop this designation and identify patients by their disease: specific amyloid disease, glomerulonephritis, lupus, etc.

DR. RILEY: What would you call our childhood type of cases?

DR. CHASIS: What we always have called them.

DR. RILEY: Nephrosis?

DR. CHASIS: We call them glomerulonephritis.

DR. RILEY: That is what I am afraid of. I would cling to "the nephrotic syndrome".

MODERATOR GOLDRING: *I think Dr. Riley wants to add another term to the classification, which he calls "idiopathic" nephrotic syndrome.*

DR. RILEY: Idiopathic is good, but, unlike Dr. Schreiner, I don't object to the term "primary" until it can be proven secondary to something.

MODERATOR GOLDRING: *Dr. Merrill, what is the value of the artificial kidney in the treatment of glomerulonephritis?*

DR. MERRILL: We have not found that it has been spectacularly useful, not because it is not *per se* an extremely effective tool for the treatment of renal failure, but for a number of other reasons. First, as has already been suggested, acute glomerulonephritis in children has a pronounced tendency towards spontaneous healing. So such vigorous treatment would not be indicated.

Secondly, mortality from acute nephritis, when it occurs, is largely, although not entirely, due to the hypertensive or fluid retention aspects of this disease rather than to uremia *per se*.

Finally, at least in our experience in adults, by the time an individual has been anuric for a week or ten days, with acute glomerulonephritis, so that treatment with the artificial kidney becomes necessary solely because of his renal failure, the prognosis is so bad that while life may be prolonged, we seldom can do anything to save him. There are exceptions to that, which, I think, prove the rule. I recently saw a child in the Children's Hospital in Boston who had had ten well-documented days of anuria with acute glomerulonephritis. A year and one half later she had regained normal renal function, as indicated by inulin and PAH (para-aminohippuric acid) clearance tests. However, this child did not require treatment with the artificial kidney. So I would conclude that there might be a rare instance in which the patient's difficulty is due primarily to renal failure, or where it may be possible to use an apparatus which can ultra-filter plasma, to remove salt and water from a patient who has been overhydrated. Other than that, we have not had frequent occasion to use such artificial methods in successfully saving patients' lives.

MODERATOR GOLDRING: *Dr. Schreiner, you have had an extensive experience with the artificial kidney. Will you answer the same question?*

DR. SCHREINER: We should define carefully what type of acute nephritis we are talking about. I would like to illustrate this point with slides.

We look at acute glomerulonephritis as a very general type of spectrum.

(Silde) Here is seen the mild case, with urinary findings detectable only with the microscope or by determination of the albumin in the urine; the slightly more severe type, with periorbital edema and pitting edema; the type with associated vascular disease, sometimes localized, sometimes generalized; the type with renal failure alone, due to diminished glomerular filtration rate; and finally the severe fulminating variety with anuria. As Dr. Merrill stated, I don't think that the artificial kidney has much of a role in any of these situations, except the rare instance of edema with overhydration or overadministration of saline, where as much as eight or nine pounds of water can be removed with the twin coil kidney under positive pressure. This is a very special group with proliferative disease on which we have been concentrating. I think anuria is a leading cause of death in the severe type of acute

glomerulonephritis.

We have 160 patients with 242 dialyses in our total series, as of this spring (1958). We have had 16 patients in the category of glomerulonephritis disease with true oliguria or anuria, most of them anuric for at least two or three days and, as Dr. Merrill intimated, the survival rate of 19 per cent is extremely low. This high mortaility rate is both distressing and disturbing. We have now reexamined our hospital's records from the beginning and studied the charts of all patients with glomerulonephritis, whether they were dialyzed or not. We have a fair and rather striking series. Even 24 hours of anuria in a patient with glomerulonephritis reduces the ultimate prognosis precipitously. It is really quite shocking. In patients who were totally anuric for as short a period as 24 hours, the ultimate prognosis is very grave. So I am actually not quite so depressed about this 19 per cent survival figure as I was before I looked at the non-dialyzed cases. I think we have probably pulled a few through by dialysis.

(Slide) This shows a patient similar to the one Dr. Merrill mentioned, a five year old boy with acute post-streptococcal hemorrhagic glomerulonephritis, who became anuric. At the time that we received him, which was, as I recall, approximately on his 8th or 9th day of oliguria, his blood chemistry determinations were as follows (and these figures indicate the chemical changes during dialysis): the BUN was 253 with reduction to 53, and recovery in the bath of 25 grams of urea and 498 mg. of phosphorus. This boy went on to a diuresis and a total recovery. It is now five years since this dialysis was done and he is quite normal in his clearance tests, with an apparently normal vascular system and no residual traces of his disease. I think that, combined with our general experience with anuric glomerulonephritis, this type of response can be credited as a favorable one, and ascribed to dialysis alone.

DR. MERRILL: I should like to reemphasize two points that both Dr. Schreiner and I have stressed. One is that it is extremely rare in our experience, and I think in Dr. Schreiner's too, for a patient to recover completely after a week of total anuria.

Secondly, by the same token, in a well-treated patient it is extremely rare to have to employ the artificial kidney within a week of onset of the episode. Therefore while the artificial kidney may be of value in exceptional cases, I think its use is not often necessary in the treatment

of acute glomerulonephritis.

DR. SCHREINER: We have found that some patients who were dialyzed remained oliguric after dialysis and this is a most disturbing situation to encounter. We have been wondering whether multiple dialyses in this type of patient may not actually perpetuate the antibody reaction by supplying fresh complement to the patient.

(Slide) We have wondered whether the reaction stops (as some people have suggested) because the patient runs out of complement and that, in providing fresh complement, as is done with fresh transfusions to prime the kidney, the proliferative lesion may actually be perpetuated.

(Slide) This man came in with a classical glomerulonephritis, with acute oliguria. When dialyzed he remained oliguric for 79 days, although he certainly would not have lived that length of time without the artificial kidney. These were the seven dialyses done in 79 days which enabled us to manage his clinical state. This patient ultimately died of acute bronchopneumonia. Nevertheless, consideration must be given to the advisability of using different procedures. We have now, on a trial basis, begun a long-term program using globulin-free blood as a means of priming the kidney in those special cases demonstrating hemorrhagic glomerulonephritis. One patient, done since then, has not become hypertensive during the anuria, the only such patient with prolonged oliguria with glomerulonephritis, and this gives us a slight glimmer of hope.

(Slide) This shows what happens to the electrophoretic pattern in a patient when this type of material is used. It contains almost no globulin and no complement. We were able to keep his complement low for the entire 80 days of his oliguric course. Although we have maintained several patients for 80, 70 and 60 days, we have not had one of these prolonged cases survive despite the prolongation of life in that period of time. The most tantalizing thing is that the kidneys do not appear too badly. During the 80-day period, the glomeruli, while markedly proliferative, are not hyalinized, a hopeful sign for effecting some relief. Our present techniques have not been completely ineffectual up to now.

MODERATOR GOLDRING: *Dr. Schreiner, I am concerned with the fact that you have spoken of anuria in acute nephritis and perhaps overemphasized its importance. In the 150 patients Dr. Chasis and I studied*

at Bellevue there were only three with anuria, with the longest lasting three days. You speak of patients with anuria for as long as a week, or was it ten days in one patient?

DR. SCHREINER: Yes.

MODERATOR GOLDRING: *Wouldn't you say that anuria is an unusual problem in acute diffuse glomerulonephritis?*

DR. SCHREINER: I think we probably collect them! We have had 16 cases of severe oliguria due to acute glomerulonephritis in the last five years.

MODERATOR GOLDRING: *By oliguria, you mean?*

DR. SCHREINER: Less than 300 ml. per day.

MODERATOR GOLDRINGS *We use less than 100 ml. per day as a standard, but I suspect the difference is not significant.*

DR. SCHREINER: Most of these patients had total anuria for a period of their disease. Actually, acute glomerulonephritis is one of the unusual situations producing total anuria. Dr. Merrill has pointed out many times that it is unusual for the average case of renal insufficiency to become anuric, which is true of cases of tubular necrosis. But in our experience we have observed cases in which several days of total anuria did occur in patients with severe fulminating acute glomerulonephritis.

MODERATOR GOLDRING: *Would you make a guess as to the probable incidence of anuria for more than two or three days?*

DR. SCHREINER: The incidence would not be significant in our hospital population. We don't see the patient until he becomes anuric. We have a highly selected patient material. It would not be analogous to the primary series found in a hospital like Bellevue.

MODERATOR GOLDRING: *We shall now extend the questions regarding the artificial kidney.*

DR. CHASIS: I wonder whether the panel intends to give the impression that the clinical appearance of the child or the adult with acute diffuse glomerulonephritis in the first week of the disease is a guide to prognosis. Are more severe symptoms, in the child or adult, more apt to result in chronicity or death than a mild episode?

DR. MERRILL: Could I answer that? I think, as Dr. Chasis is probably implying, that the correlation is an inverse one. In fact, it seems to me the child with the more acute attack (barring anuria for a period of time), almost tends to do better, which is why I would support the antikidney antibody reaction. Certainly nothing can be said about the

prognosis, in terms of the severity of the initial clinical picture, apart from the duration of the anuria.

DR. SCHREINER: We would tend to agree that there is no close correlation between the clinical picture and the prognosis, except when severe oliguria or anuria has occurred. This is a recent development resulting from our survey of these cases, and leads us to expect a much poorer prognosis if actual anuria exists, even for 24 hours.

To answer our previous question: In seven years 158 cases were admitted with acute glomerulonephritis, 15 of them with severe oliguric anuria, an incidence of almost 10 per cent.

MODERATOR GOLDRING: *Dr. Schreiner, to continue with the artificial kidney question: What about its use in acute renal insufficiency?*

DR. SCHREINER: Here we feel considerably more enthusiastic.

(Slide) We have divided our dialyzed cases into acute renal insufficiency or acute tubular necrosis of varied etiology. This was crush syndrome, postpartum shock, kidney, etc., and separated from the group of identified poisons, which would include bichloride of mercury, barbiturates, sulfa drugs, heavy metals, etc. In our over-all group of renal insufficiency we now find our ultimate survival rate to be 36 per cent, up from the 33 per cent figure shown on the slide. This is in terms of survival, and assuming responsibility for all mortalities. A great many figures are quoted in an attempt to separate deaths due to the kidney situation from those due to other factors. We had difficulty doing that, so we determined survival as the point at which the patient left the hospital to go home, which is the barest definition you can have. Of the patients with nephrotoxic injury, 53 per cent have survived. This represents a selected group, of course. Conservative management of fluid-electrolyte problems is employed for as long as we feel it benefits the patient. We dialyze only a decided minority of patients with acute renal insufficiency who are referred to us. In selecting the more severe cases for dialysis we do so in the belief that this type of long survival rate is fairly good evidence that the artificial kidney does contribute something in the management of these cases with acute insufficiency.

(Slide) This patient with the crush syndrome was managed by a man skilled in handling fluid and electrolyte balance. Despite good, conservative management, the patient's condition deteriorated rapidly and he slipped into coma on his sixth oliguric day. Urine output was slightly over 400 ml. per day for one or two days, but a staphyloccocal

enteritis and septicemia appeared in the middle of the course. At the 30th day there were two days when he excreted one liter of urine. In his initial mental state he was quite disoriented and he had muscular twitchings. After the first dialysis he appeared more oriented, then again became lethargic. Following the second dialysis he recognized his wife and brother but again became semi-comatose. After the third dialysis he became awake but later developed Cheyne-Stokes respiration and again became confused and lethargic. In all, six dialyses were carried out on this patient, and he did not really develop diuresis until the 42nd day. After the fifth dialysis he appeared mentally clear, and finally, following the sixth dialysis, he was on the road to recovery and is now back at work. We submit, first of all, that if we had already exhausted our therapeutic resources on the sixth day, we could not have maintained such a patient for a 40 or 50 day period without the artificial kidney, nor is there any natural history of acute renal insufficiency which would permit us to say that a patient went into and out of coma, six times on the day preceding and the day following dialysis, by coincidence. In our opinion this type of patient demonstrates unequivocally the value of the artificial kidney in the treatment of acute renal insufficiency.

MODERATOR GOLDRING: *Dr. Chasis, how do Dr. Schreiner's results compare with yours, using treatment other than the artificial kidney, and will you describe the treatment you prefer?*

DR. CHASIS: Our experience is limited and I don't think that I would like to compare statistics. We use conservative measures that attempt to control fluid, calorie and electrolyte balance. Most of the patients we see are relatively mild examples of acute renal failure, and our recovery rates are comparable to those of Dr. Schreiner's, that is, about 50 per cent.

I am concerned, however, about comparing statistics. I do not believe that renal insufficiency of itself kills very frequently. In the majority of patients with acute renal insufficiency death is due to the associated disease and I think that Dr. Schreiner has taken the first step and broken them down into categories. We do not have enough information at this time to choose between the two, that is, between so-called conservative therapy and therapies that use dialysis in one form or other. It is unfair to compare recovery rates in patients who have had six or seven hours of extensive abdominal surgery for carcino-

matosis with patients who have had an overdose of carbon tetrachloride. I don't know of any series that could be analyzed so as to permit one to say that, if conservative treatment were instituted early and properly carried out, it could not have prevented the kind of death that one associates with uremia.

MODERATOR GOLDRING: *Would you define, in a little more detail, what you mean by conservative treatment?*

DR. CHASIS: The conservative treatment of acute renal failure depends upon rigid control of fluid, calorie and electrolyte balance.

Just enough water should be given by mouth or vein to cover insensible water loss, which amounts to about 750 ml. per day, less water of oxidation which supplies roughly 300 ml., i.e., 500 ml. per day, to which should be added the amount of fluid lost from the body in urine, sweat, stool and vomitus. The patient is weighed daily so that a gain in weight indicative of excessive fluid administration will be detected. The fluid is given *per os* or as an infusion of 20 to 50 per cent glucose through a polyethylene tube into the inferior vena cava.

Calories are provided by electrolyte-free, nitrogen-free glucose or fat, in an amount which will prevent excessive body protein breakdown. One hundred grams of glucose are given daily with or without additional calories in the form of oral fat emulsion.

Electrolyte and pH control of the anuric patient begins with this control of water intake and an adequate supply of calories. Should excessive retention of acid occur, as indicated by clinical symptoms and significant quantitative changes in the serum, oral or parenteral bicarbonate may be cautiously administered. Oral administration of 10 to 20 gm. of sodium bicarbonate in the first 24 hours is the average dose. There is danger of respiratory alkalosis if excessive alkali is given.

No other electrolytes are given unless indicated by clinical manifestations of deficit, low plasma levels, or known loss through the gastrointestinal tract or skin. The plasma sodium concentration is extremely variable; the explanation for hyponatremia is not apparent; administration of hypertonic saline may produce pulmonary edema. Therefore, it is wiser to administer sodium as normal saline, if at all. Hyperkalemia will probably not occur if excessive body protein breakdown and acidosis are prevented. If it develops, cation exchange resins may be given orally or rectally to control it; dialysis offers a mode of management if hyperkalemia does not respond to conservative measures.

Once diuresis is initiated, indicating progress toward recovery, the patient must still be managed according to the principles outlined. During this phase of the disease such manifestations as hypokalemia and hypochloremia should be watched for and, if necessary, treated by appropriate oral or parenteral administration of electrolyte.

In general, in the kinds of patients we see, we can carry them in this way for as long as two to three weeks of anuria without too much change in the clinical appearance of the patient.

MODERATOR GOLDRING: *Dr. Merrill, what is your opinion of the artificial kidney in acute renal insufficiency?*

DR. MERRILL: About a year ago Dr. Schreiner and I attended a meeting at which people from all over this country and from Europe discussed the artificial kidney and compared statistics. I believe I can speak for him and the others, since our conclusions on the statistics were pretty much the same. I am pleased to learn that Dr. Chasis does not like to compare statistics, as I quite agree that they should not be compared. Renal insufficiency certainly covers a wide variety of diseases or clinical syndromes, most of which are complicated by severe trauma or surgical procedures, and I do agree that the end event frequently is brought about by infection or the trauma itself. But I should like to emphasize a few points.

First, one should not compare conservative treatment and dialysis, because both methods are used by people like Dr. Schreiner and myself. We have treated over 400 patients with acute renal insufficiency, and have used the artificial kidney in less than half of these cases. This, perhaps, gives those of us who have an artificial kidney available, a larger series and thus a greater experience with conservatively treated patients than is the case with most physicians. We agree that the results of the two modes of management should not be compared. The artificial kidney should be used as an adjunct rather than as an alternative to good conservative management. If you have an artificial kidney, numbers of patients with acute renal insufficiency are referred to you and these provide a large experience in the use of conservative management on a selective basis.

Attempting to compare mortality is a little like trying to compare mortality with and without blood transfusion. The sickest patient ordinarily receives the most blood, and if one compares only those two factors (mortality or survival and volume of blood received) it appears

obvious that transfusion is a lethal form of treatment.

It is true that our patients do not die of uremia *per se*, either with or without the artificial kidney. I am convinced (and Dr. Schreiner's slide and a good many of our cases bear this out) that chronic, severe, debilitating uremia potentiates infection and potentiates aspiration pneumonia. It similarly potentiates a number of other lethal situations which beset the sick, bedridden, semi-comatose patient, situations which are ameliorated by the artificial kidney, which can increase the level of awareness and facilitate conservative management. I again make a plea for using the two in conjunction rather than as alternatives.

DR. SCHREINER: It does make good sense to try to keep the patient in the best possible clinical condition for the longest period of time, if one is trying to ward off the leading causes of death. In our experience, as Dr. Chasis intimated, there are the complications of uremia, with infection the principal enemy in our institution. During periods of skepticism, which alternate with periods of enthusiasm, we have often tried to maintain patients with conservative measures for long periods of time. I honestly believe a few have been lost as a result of trying too hard. Increasing experience makes it even possible to recognize and select the prolonged type or the patient with the high catabolic rate who will not be able to survive for long periods of time.

Although no two patients are alike, I think some general categories can be established, one of which is to think of these patients in terms of their catabolic rate. The patient who, with a constant body water, is increasing his BUN increment by 4 to 8 mg. per cent per day must be managed clinically in quite a different manner from the patient whose BUN is increasing 60 mg. per cent per day. Therefore, when one speaks of keeping a patient alive five or ten days, it has no significance without definition in terms of protein breakdown, which, we believe, correlates directly with the speed with which the disease progresses.

In Korea men died of hyperkalemia within 24 hours. We don't see this type of patient very often in our practice. As Dr. Chasis has intimated, it is also difficult to find a control series.

At the meeting that Dr. Merrill mentioned, it was stated that the only person with a large series who actually had a good renal laboratory established before he had acquired his artificial kidney was G. Richet in Paris, and he was able to show a substantial decrease in mortality after an artificial kidney was added to an already going team.

The same phenomenon was observed in Korea. The mortality rate from acute renal insufficiency was extremely high before a team of knowledgeable people was put in charge. When a properly trained group, with good laboratory facilities at its disposal, became available, a big drop in the mortality rate followed, from 80 to 90 per cent down to 50 to 60 per cent, with a further drop, as I recall, to about 40 per cent mortality after an artificial kidney was added to the group. If you start *de novo*, the most important requirement is to have trained people and good facilities, but I do think there are still some patients who, regardless of this, cannot be satisfactorily managed without dialysis.

MODERATOR GOLDRING: *Dr. Schreiner and Dr. Merrill, have you more enthusiasm for the use of the artificial kidney in acute renal insufficiency than in acute glomerulonephritis?*

DR. MERRILL: I certainly do, yes.

MODERATOR GOLDRING: *Dr. Riley, I have an easy question for you. Has the artificial kidney any place in the treatment of the nephrotic syndrome?*

DR. RILEY: Having no artificial kidney at my disposal I cannot speak from actual experience. Had I one, I cannot conceive of using it.

Before leaving this subject, may I ask Dr. Chasis what kind of measures he would use to try to control hyperkalemia?

DR. CHASIS: I think that if the renal lesion is recognized early and the condition is not associated with complications, hyperkalemia is rarely a problem. If the patient is afebrile, if he does not have a serious infection, if it is just a question of a post-transfusion reaction or carbon tetrachloride intoxication, if the caloric intake is maintained, there is no reason for the accumulation of potassium, unless some well-meaning person comes along and gives the patient orange juice.

MODERATOR GOLDRING: *By maintaining the caloric intake, you mean with glucose?*

DR. CHASIS: With glucose, and, in some instances, supplemented by fat.

MODERATOR GOLDRING: *Dr. Chasis, in the treatment of chronic nephritis it is common practice to be guided by the electrolyte pattern of the blood, especially when there are disturbances in sodium, potassium and chloride balance. Do you approve of this as a general rule?*

DR. CHASIS: I have a very short answer. Our practice is to treat disturbances in potassium, sodium and chloride balance only when there

are symptoms or signs associated with the disturbance.

MODERATOR GOLDRING: *Are there any further comments from the panel on this very important question?*

DR. SCHREINER: I think a good many of those changes are often iatrogenic and preventing them is as important as treating.

DR. MERRILL: There are some situations in which abnormalities of the electrolyte pattern of the blood reflect the underlying disturbance rather than act as causative agents. In such instances the underlying disturbance should be treated, rather than the serum sodium level alone. The classic example of this is the anuric patient who has received too much water. If you fill up with sodium, simply to raise the serum sodium, you produce acute pulmonary edema. The treatment for hyponatremia in such a case is not to correct the sodium by adding sodium, but to reduce water intake.

DR. RILEY: I notice in the question that emphasis is placed on sodium, potassium and chloride. What would the other panelists say about calcium and phosphorus, which, I think, become rather a problem with the chronic, failing kidney, particularly in growing children?

DR. MERRILL: I would like to try to answer that. It is a problem we have tried to solve for a long time. Frankly, I don't know the complete answer. Aluminum hydroxide gel has been used in special ways in an attempt to remove phosphate. Although we have had some success, on the whole this method has not proved too satisfactory. In patients with chronic nephritis, our experience would indicate that the calcium level, *per se*, is seldom the cause of symptomatic difficulty. Whether the resulting decalcification is related to the serum calcium level, I do not know. Interesting results, which seem to indicate that this is not so, have been obtained by Dr. Howard of Baltimore. In his experiments he was unable to calcify rachitic rat's bone and cartilage cultivated in normal urine with a calcium phosphate product far in excess of that necessary to calcify bone. Perhaps, then, the levels are not solely responsible for the condition. On the other hand, Scholl's solution (calcium and vitamin D) proved to be effective in some instances when administered to children. However, I believe adverse side effects, such as metastatic calcification, have been reported.

Could I ask Dr. Riley to answer his own question in that regard?

DR. RILEY: I have found that some of our children with chronic, failing kidneys become more comfortable when given something to

absorb phosphate. The aluminum hydroxide gel type of treatment seems to do two things. One, it tends to lower the phosphate level in the blood to a degree, though not to a very great degree. Two, it also tends to correct acidosis to a small degree and thereby seems to make the patients feel better clinically, which in turn may account for a slight increase in life expectancy.

DR. SCHREINER: This has been true in our experience also. I should like to add a word of caution in treating hypocalcemia. Many physicians exhibit a therapeutic reflex when they encounter a slightly decreased serum calcium and automatically administer calcium gluconate. In these patients the phosphorus level is apt to be quite high and it may be dangerous to give them large amounts of calcium. First, in this situation one cannot maintain the serum calcium level for more than a short period of time by administering exogenous calcium. Secondly, one may exceed the calcium-phosphorus solubility product and produce deposition of calcium crystals in the kidney, which we have seen in patients so treated, and also in other organs of the body. I think this can be a potentially dangerous situation. With very high phosphorus levels, I believe it is more rational to do as Dr. Riley and Dr. Merrill suggest, to try to lower the phosphorus.

My understanding of the action of aluminum hydroxide gel is that it primarily removes the phosphorus present in the diet and is not nearly so effective in removing or producing an exchange of phosphorus across the mucosa.

One should also not forget that phosphorus can be lowered by proper choice of food or by intravenous feeding in an acute situation.

MODERATOR GOLDRING: *Dr. Riley, what results have you had with hormone treatment of the nephrotic syndrome?*

DR. RILEY: I can illustrate this quickly with slides.

(Slide) This represents a survival curve of patients with the nephrotic syndrome before 1950, and the construction of the diagram is that, at onset of the disease, there is, of course, 100 per cent survival. Progressing outward from onset of the disease, there is a gradual reduction in surviving patients. Six or seven years after the onset, the survival curve is about 50 per cent. These represent patients at a time before the steroids were available. I think it is important not to speak of the nephrotic syndrome in terms of a single mortality rate because it is a disease, like cancer, that terminates in death over varying periods, from a few

months to many years.

(Slide) This pair of curves is similar to the previous one. Here Curve B is taken from controls with onset of their disease between 1946 and 1950, before any steroid therapy was readily available, so presumably these patients could not have had much in the way of steroid treatment. Curve A, on the other hand, is taken from patients whose onset began after 1952 and presumably shows the effects of increasingly intensive treatment with steroids. The difference in the curves, four years after onset, is highly significant statistically. Also, I think all of us who have worked in this field are convinced that steroids do accomplish something more than just produce a diuresis. They actually prolong life. What is going to happen in the next 10, 15 or 20 years I won't predict. One can only be hopeful.

(Slide) This slide represents a small sample of our patients at the Babies Hospital. The previous two slides were composed of pooled figures, so their statistical significance is much greater than this from our group at the Babies Hospital. This represents the status of patients four years after onset of disease in the two groups, the one in the pre-steroid days and the second in the present era. The categories are: 1) no disease, 2) only proteinuria, 3) minimally active disease. Thus, these first three represent patients not handicapped by the disorder. The percentage thus represented is far greater now than formerly. So not only are the patients living longer but those alive are less troubled by the disease.

DR. SCHREINER: Would you agree, Dr. Riley, that we should still be cautious in hazarding a favorable long-term prognosis? I am somewhat disturbed by our recent experiences of recurrent disease in two patients, one five years and the other five and one half years after total remissions, and totally negative urines.

DR. RILEY: I agree fully. In the days when many patients did not survive, when a few went on to apparent complete recovery, one could then be convinced that these probably would, with rare exceptions, remain well. Now, when they get well with the aid of steroids, I think all of us are beginning to see more and more relapses after long intervals of apparent good health. On the other hand, I have been happy that these patients who have relapsed have subsequently responded again to treatment.

DR. MERRILL: That has been our experience exactly, which makes

me feel a little more hopeful.

MODERATOR GOLDRING: *Dr. Merrill, a burning question these days is the one that you brought up some years ago, the question of kidney transplantation. Will you tell us something about it?*

DR. MERRILL: Yes. I have been asked about the indications for and the results of kidney transplantation. I think I can answer those questions very briefly and then go on to consider what we can reasonably hope for in the use of this procedure. First, the indications for kidney transplantation. At the present time, the only clinical ones are in identical twins, one of whom must have a normal genitourinary tract, with no contrary indications to surgery, while the other twin is terminally ill with chronic renal failure. We have done nine such cases. Two others have been done elsewhere and of these 11 cases eight are alive and quite well.

One of our cases failed because of an abnormality of the renal artery which could not be anastomosed. The other two were fascinating in that both of these patients developed glomerulonephritis in the transplanted kidney, presumably facilitated by some form of circulating antibody. We have also done some 23 homograft transplanted kidneys from non-related individuals, taken from cadavers or at the time of other surgical procedures in sick patients. None of these have worked for any great period of time, but at least one of them did work reasonably well for five and one half months.

(Slide) This shows how kidney transplantation is a feasible procedure in identical twins. You can see the ureter functioning well in normal intravenous pyelograms, a year and one half after transplantation. The dividends from this were twofold. Not only did the patient's renal failure improve but malignant hypertension disappeared. We took out his two diseased kidneys. So if we can succeed in doing this again we shall have a double dividend.

(Slide) Now the problem in non-identical twins. We approach this problem first by learning something about the transplantation-rejection response, which is the same for skin as it is for the kidney, and presumably for any other organ. This, in other words, is an individual-specific response. B will slough any tissue from A. It does not make any difference what kind of tissue, and presumably rejection occurs because some sort of antigen gets to a regional lymph node, produces a sensitized lymphocyte-containing antibody (although none has been demonstrated

in the classical sense) which is then responsible for the rejection of the transplanted tissue. This applies equally well to the kidney.

(Slide) There are two practical or possible approaches to the problem in the clinical realm, based upon animal experiments. The first is this: if one knocks out all antibody-forming tissue with lethal whole-body x-ray and enables the animals to survive by the transplantation of bone marrow (since all hematopoietic tissue is also knocked out), the bone marrow then becomes a tissue living and growing in animal B. Since animal B will tolerate animal A bone marrow, B will also tolerate skin and kidney from A. Preliminary experiments of this nature have been done in man. Drs. Thomas and Ferrebee have done this 23 times in the human with leukemia. We have done it twice in individuals whose single kidney had been removed by mistake. We have not had success although in one instance it looked as though the bone marrow did "take". However, we did have success in 36 per cent of the rabbits on whom this was done, so it may be a question of getting the right amount of bone marrow or the right amount of x-ray. Only time will tell.

DR. SCHREINER: Are you satisfied with any human case of human transplant of bone marrow?

DR. MERRILL: There are unquestionably temporary takes of bone marrow, none of them permanent.

The second approach is to desensitize the recipient by injecting him with antigen from the donor in order to neutralize antibody. This is a classic immunological technique. If we ever succeed in determining the exact tissue antibody we might be able to accomplish this. We have been able to do it in disseminated lupus erythematosus and reverse the fixation of fluorescent globulin. This may prove to be a feasible approach. However, the answer to the original question is that, to date, the procedure is purely experimental and holds little hope for success.

MODERATOR GOLDRING: We shall leave that for the moment. *Dr. Riley, what is your opinion of the value of prophylactic antibiotic treatment in the prevention of exacerbations of glomerulonephritis, and therefore, presumably, its chronicity?*

DR. RILEY: I regret to say, Dr. Goldring, that this is strictly opinion. It is my belief that acute nephritis is presumably the result of a peculiar reaction to streptococcal infection, and since during the recovery phase of acute nephritis a relapse is often associated with a clinically obvious

throat infection, it would seem logical to maintain a patient on antistreptococcal medication until all signs of nephritis have subsided. This has been my practice.

DOCTOR: For how long would you continue antistreptococcal medication?

DR. RILEY: Until all signs and all the urinary abnormalities have subsided.

SAME DOCTOR: Till 15, 16 years of age?

DR. RILEY: In most patients it would be only a matter of six months or a year, or however long it takes for the urine to clear. On the other hand, the incidence of such relapses during the course of recovery from acute nephritis is so small that one would have to have a series running into the millions to get significant statistics in the different results. So it would be extremely difficult to prove the value of this course of therapy. I do use antistreptococcal medication during the recovery phase, but I cannot claim any scientific evidence that this is useful.

MODERATOR GOLDRING: *The question is of such importance that I think each member of the panel ought to express an opinion on it. Dr. Chasis, will you take it next?*

DR. CHASIS: In chronic nephritis, as Dr. Merrill indicated earlier, we don't know the cause of chronicity. We don't think that there is any evidence that would make the streptococcus the culprit in more than the initiation and exacerbation, nor do I think any one believes chronicity in the disease is due to continued infection. Antibiotic therapy therefore would have a limited target; one would be attempting to prevent exacerbations in the disease rather than the progress from acute to chronic nephritis. One would have to weigh the benefits derived from preventing exacerbations during the course of disease against possible difficulties and potential dangers of maintaining patients on antibiotics for five, ten or 20 years. At this point we do not administer antibiotics prophylactically to patients with chronic nephritis.

MODERATOR GOLDRING: *Dr. Merrill!*

DR. MERRILL: Two things should be considered. It has already been said that classical, acute glomerulonephritis tends to heal and probably does not recur and that it is associated with type-specific antibodies. Therefore antibiotics would not be used in this situation.

Furthermore, the chronic state is not associated with immunologic antibodies in the classic sense. We believe that there are antibodies but

they are not specific for the streptococcus. They may be incomplete antibodies.

The action of penicillin is to kill organisms after they have attained a certain stage of growth. With a sensitivity glomerulitis, the amount of streptococcal antigen needed to initiate that effect is infinitesimal and certainly penicillin could not prevent it. Penicillin will control the invasive characteristics of streptococci, but by its very nature will not prevent its growing and liberating enough antigen to do harm in terms of immunologic reaction. So, while we use it in patients with sore throats and chronic nephritis, we really have not seen any very good results from its use in this field.

DR. RILEY: May I just clear up one point? I was talking about what I do with cases of acute nephritis. Once I become convinced that the acute has merged into chronic nephritis I no longer continue the antibiotic.

MODERATOR GOLDRING: *Dr. Schreiner!*

DR. SCHREINER: I think this can definitely be taken out of the realm of science because even in rheumatic fever it has been extremely difficult to get proof that prophylaxis was valid, and this proof has been obtained only by getting a large pooled series. But rheumatic fever, as Dr. Merrill mentioned, has a constant attack rate. Glomerulonephritis does not have a constant one. There are streptococcal infections in which the incidence of glomerulonephritis is zero. Germany reported 19 per cent and some higher. Any statistician will say it is obvious that, if there can be an attack rate of zero, it is impossible ever to get a large enough series in the whole world or its sister planets that would have statistical significance in any one outbreak of streptococcal disease because it could never be proved with statistical significance that anything had been done. So I think that this is an impossible experiment, and time should not be wasted on it.

It depends on the doctor's inclinations and he has to argue by analogy. There are series in children, for instance, as in those reported from Duke University, with 10 or 15 per cent of glomerulonephritis due to recurrent skin infections, while we see other children who have four or five "hot" ears a winter with otitis media. It appears that every time they get a cold it is accompanied by a secondary bacterial infection. Such a child might conceivably be benefited by being carried on antibiotics. However, it cannot be proved statistically.

DR. CHASIS: I don't think we mean to infer that infection should not be treated with antibiotics. I thought the question was directed at the use of antibiotic therapy in established glomerulonephritis.

DR. SCHREINER: A patient with glomerulonephritis with recurrent infection might be kept on penicillin for months or perhaps a year, based on the supposition that the total exposure is being reduced, but it is difficult to be certain what is being accomplished, as Dr. Merrill pointed out.

MODERATOR GOLDRING: *Dr. Schreiner, do you advise the use of antibiotics as a preventive measure after the first attack of glomerulonephritis?*

DR. SCHREINER: I don't think it can be so advised, on a scientific basis.

MODERATOR GOLDRING: *Do you personally use it?*

DR. SCHREINER: Only in the case where I get a history of an established pattern of recurrent bacterial infections.

MODERATOR GOLDRING: *You don't use it routinely?*

DR. SCHREINER: No.

MODERATOR GOLDRING: *What is your opinion of the value of sensitivity tests in selecting the proper antibiotics for the treatment of pyelonephritis?*

DR. SCHREINER: I think one must first appreciate what a sensitivity test is, as usually carried out in the hospital. It determines the zone of inhibition from a prepared disc soaked with antibiotic against the organism grown out in artificial culture. It is obvious that this may bear no relationship at all to the biologic conditions in the patient. It depends upon a wide variety of circumstances. It has been shown, for instance, that discs from different manufacturers differ considerably in their concentration of antibiotic. Second, the performance on agar plate is probably better than anything else, when tied in with the solubility of antibiotic in agar. Third, the organism observed in subculture may be, and usually is, the one that grows out the first day and *may not* be the one that is producing the pyelonephritis, which may not grow out till the third day. I think we, as clinicians, have overbought the value of sensitivity discs in deciding our therapy. In many places I have seen this as an automatic response,—if the disc says chloramphenicol, it has to be chloramphenicol. Nothing else can be used. In general, particularly if carried out with a tube dilution method, the sensitivity test may indicate the presence or absence of organisms that have had pre-

vious exposure to groups of antibiotics, but it should not be used as more than a general guide, especially so if good clinical results are obtained with an antibiotic, for instance as we frequently do with chloramphenicol, in cases where the disc shows resistance to chloramphenicol. I think the performance in the biologic situation is more crucial to the patient than the performance of the disc.

MODERATOR GOLDRING: *Dr. Merrill, will you comment on that question?*

DR. MERRILL: I would agree in general on that. One way of checking the laboratory, in the situation discussed by Dr. Schreiner, is to do a Gram stain on freshly voided urine. If, on Gram stain of fresh concentrated urine, no organisms are seen, or if one sees organisms which do not jibe with the culture plate, one can be quite sure the profuse growth reported by the laboratory is probably not the cause of acute urinary tract infection.

MODERATOR GOLDRING: I am sorry we cannot get to all of the questions but we will take them in order. *Dr. Merrill, are potassium retention and the consequent symptoms of hyperkalemia seen in the absence of oliguria?*

DR. MERRILL: Yes, they may be. In general, oliguria is the *sine qua non* for potassium retention, but there are situations in which patients who are loaded with potassium, parenterally or by mouth, may not excrete because of a sudden load and exhibit the signs and symptoms of potassium intoxication. In general, however, unless potassium is given by vein, a patient with good urine volume output does not have clinical difficulty with hyperkalemia. I emphasize this because in many patients with chronic renal failure potassium is drastically restricted. Here the elevation of potassium we referred to a short time ago is the *effect* of renal failure, not its *cause*, and there is no real necessity for restricting these patients because of a slight elevation of serum potassium.

MODERATOR GOLDRING: *Dr. Schreiner, is there any value in long-term intermittent perfusion of an isolated segment of ileum in a patient with chronic renal insufficiency?*

DR. SCHREINER: We don't have any data on this. In San Francisco Dr. Schloerk was perfusing a segment of the large bowel as well as the ileum. There is one major defect in such perfusion. The bowel mucosa is almost totally unable to secrete uric acid. So one patient, who was maintained very well in terms of his acid-base balance, died

of uric acid nephritis, with symptoms of gout and with marked increase of serum uric acid. I think this is something that needs further exploration. Perhaps perfusion, coupled with occasional dialysis to take care of the uric acid, could maintain a chronic patient. The total number of patients done to date is too small to permit a reasonable analysis or conclusion as to whether this will really be worth while. It is a tedious performance, in terms of controlling the rate of fluid administration.

MODERATOR GOLDRING: *Dr. Riley, does aldosterone retention play any role in the edema of nephritis or the nephrotic syndrome?*

DR. RILEY: It plays a role in the nephrotic syndrome. I don't know of any studies done in acute or chronic nephritis. In the nephrotic syndrome it has been shown that during the phase of retention of edema there is a tremendous increase in aldosterone output in the urine. It would seem likely that this is a secondary phenomenon associated with the accumulation of edema, rather than having any primary role in producing retention of edema.

MODERATOR GLLDRING: *Dr. Chasis, this question is addressed to you: What do you do about hyperlipemia?*

DR. CHASIS: In chronic nephritis hyperlipemia is rarely seen. In acute nephritis it presents no problem but in the nephrotic stage of glomerulonephritis it does, and there isn't anything I know that can be done about it.

MODERATOR GOLDRING: The next question: *Has any member of the panel seen instances of the nephrotic syndrome associated with acute or chronic pyelonephritis?*

DR. SCHREINER: There is one patient we reported in our series who was admitted with staphylococcal enteritis, a severe interstitial pyelonephritis and myocardial infarction. He had actual bacteremia and septicemia. This was a real oldfashioned interstitial nephritis with the whole interstitial area of the kidney infiltrated with polymorphonuclear leukocytes. If one wishes to consider this a broad variant of pyelonephritis, as we would, he did have the nephrotic syndrome associated with his disease. However, we found in a number of such patients with this type of fulminating pyelonephritis that they have actual focal changes in the glomeruli. This patient had basement membrane changes in addition to the pyelonephritic picture. I also recall another patient, under the care of a friend of mine, who has pyelonephritis and the nephrotic syndrome.

MODERATOR GOLDRING: *You are indicating it is not common?*

DR. SCHREINER: Very rare,—in general, one of the few things which does not cause the nephrotic syndrome.

MODERATOR GOLDRING: Now let us have two or three quick answers. *Dr. Merrill, how long do you treat the first attack of pyelonephritis, to prevent chronicity?*

DR. MERRILL: That is an extremely difficult one to answer. We would prefer to treat such a patient for a minimum of three weeks with an appropriate antibiotic, then to follow him for a minimum of two weeks, to be sure that urine cultures and urine examination revealed no recurrence of infection, and follow him for another six months or a year, at one month intervals. That is the minimum. The maximum, of course, can be anywhere up to five years.

DOCTOR: *With or without x-rays?*

DR. MERRILL: If the urine were completely clear I would not suspect there was anything going on to change the x-ray picture. Obviously, of course, the first thing to be done in any patient with pyelonephritis should be to rule out any obstructing pyelo-uropathy.

MODERATOR GOLDRING: *Dr. Schreiner, before we close the meeting, will you discuss peritoneal dialysis versus the artificial kidney?*

DR. SCHREINER: There are actually several methods of peritoneal dialysis which have been proposed, Dr. Grollman's, that of Dr. Merrill and colleagues, and Dr. Paul Doolan of Oakland, California, who is now using a method which involves the surgical placement of tubes into the peritoneal cavity under direct vision. I think he has perhaps the best exchange figures that have been presented to date, but under any circumstances the method is considerably less efficient, timewise, than the artificial kidney and it requires the better part of a day to dialyze that day's accumulation; consequently this process becomes a very difficult one to continue for long periods of time.

MODERATOR GOLDRING: Thank you all very much, both panel members and audience, for your participation in this discussion.

CUTANEOUS NEVI, COMMENTS AND COMMON MISCONCEPTIONS CONCERNING THEIR MANAGEMENT*

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AMONG the more common cutaneous lesions affecting man, those most likely to cause serious concern are certain of the pigmented and vascular nevi. Because of the importance of these particular nevi to individuals of all ages, regardless of sex or vocation, and because of the responsibility concerning these lesions that must be shouldered by the physician consulted, whether general practitioner or specialist, I have chosen to comment briefly on some of the more common misconceptions regarding the management of the more frequently encountered pigmented and vascular nevi. My discussion is based on recent publications prepared with Dr. Alfred W. Kopf[1] and Dr. Rudolf L. Baer[2], my colleagues in the Department of Dermatology and Syphilology of the New York University Post-Graduate Medical School.

I hope that, by discussing what I believe to be important "misconceptions", I shall be successful in dispelling some of the errors which have made their way into medical thinking, and as a result of which there may be errors in the management of these lesions.

Cutaneous nevi result from prenatal malformations, or, stated another way, are congenitally determined circumscribed new growths which may be present at birth, may appear shortly thereafter or any time later in life. The latter are referred to as delayed or tardive nevi.

PIGMENTED NEVI

Of the pigmented nevi, only those containing nevus cells, and which I shall refer to as nevus-cell nevi, will be discussed in that these are the ones that may prove of medical consequence. Nevus-cell nevi are of three types: 1) junction nevi; 2) compound nevi; 3) intradermal nevi.

Unfortunately, the gross features of nevus-cell nevi are not sufficiently typical to permit easy and accurate recognition. It is only

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through experience and a knowledge of the clinical characteristics of these lesions that any degree of proficiency can be achieved in establishing the correct diagnosis.

In general, *junction nevi* are usually tan to dark brown, and even blue to black, and the pigment is often mottled in distribution. The lesions are ordinarily flat to slightly elevated, smooth and usually without dark coarse hairs. They vary in size from 1 millimeter to several centimeters and may occur anywhere on the body, although they are most common on the face, extremities (including palms and soles) and upper chest and back.

Compound nevi may easily be confused with junction nevi because of the similarity of clinical characteristics, but unlike junction nevi, compound nevi are usually raised and may be either smooth or verrucous. At times they may resemble intradermal nevi although they are likely to be somewhat more darkly pigmented and flatter.

Intradermal nevi may appear skin colored or may have any gradation of pigment to dark brown; here, too, the pigment may appear mottled. The lesions are almost always distinctly elevated, being dome-shaped, polypoid or pedunculated and may or may not contain dark coarse hairs. They differ in size from 1-2 millimeters to 1 centimeter or larger, and may occur anywhere on the body surface, with a predilection for the face.

A word or two about the natural history and the histopathology of these cellular nevi should be both interesting and helpful in establishing the clinical diagnosis. It has been shown that in prepubertal children over 90 per cent of these nevi have junctional elements[3] whereas in adults only about 12 per cent contain such junctional activity[4]. This change in incidence and type of nevus can be explained by the series of events which take place with the growth and maturation of the individual. In the embryonic development of the fetus, the melanoblasts migrate from the neural crest to the basal layer of the epidermis and later are transformed into melanocytes and nevus cells. When these nevus cells come together in groups and are found mainly at the junction of the epidermis and dermis, that is, at the basal layer, the lesion is referred to as a junction nevus. In time, the nevus cells drop down from the basal layer to become located entirely within the dermis, and the lesion is designated an intradermal nevus. When the nevus cells are located at the junction of the epidermis and dermis as well as in the dermis, the lesion is known as a compound nevus.

The classification of Shaffer[5], which attempts to correlate the clinical and histopathologic findings of these lesions, may simplify and be of aid in making the correct diagnosis. According to Shaffer, plain, flat, pigmented nevi occurring before 30 years of age, and speckled, flat, slightly elevated and/or verrucoid nevi or those presenting an elevated central portion with a peripheral flat or slightly raised pigmented zone usually have junctional elements. On the other hand, flat, pigmented nevi in persons 30 years of age and older and those nevi which are polypoid, dome-shaped, sessile or pedunculated are, in most instances, intradermal nevi. At all ages, pigmented nevi on the palms, soles and anogenital region are, in all probability, junction nevi.

But why all the concern about the nevus-cell nevi? Why are they so important? Because it is only the junction and compound nevi which are known to have the proclivity to undergo malignant transformation into malignant melanomas. It should be pointed out, however, that according to estimates only one in a million nevi transforms to malignant melanoma[6]. If, as has been estimated, each individual has 20 nevi then only one in 50,000 persons will develop a malignant melanoma. Nevertheless, if malignant transformation from either the junction nevus or compound nevus can be avoided every precaution should be exerted. But there are certain misconceptions associated with this concern for these potentially malignant lesions. Among these are:

Misconception 1: If all nevus-cell nevi were excised prophylactically, the development of cutaneous malignant melanomas would be prevented.

Such an approach is not feasible because of 1) the impracticability of excising the conservative estimate of 3 billion 500 million nevi from persons in the United States alone, and 2) the fact that only 25-50 per cent of malignant melanomas of the skin would be prevented if excision of all the pigmented nevi could be accomplished, because a large percentage of malignant melanomas have their origin at sites clinically free of existing nevi[7].

Misconception 2: All nevus-cell nevi of the palms and soles should be excised.

Based on past figures which reported less than 1 per cent incidence of pigmented nevi on the palms and soles[8] and the therefore apparently high incidence of malignant melanoma developing from nevi at these sites, particularly the soles, excision of all such lesions has been widely

TABLE I.—INDICATIONS FOR THE TREATMENT OF NEVUS-CELL NEVI

Treatment Mandatory

1. Nevus-cell nevi which have undergone changes or have shown "activity" such as: sudden enlargement, bleeding, inflammation, alteration in color (either darker or lighter), ulceration, crusting, development of satellite pigmented areas, or those which become symptomatic (especially pruritic or painful).
2. Nevus-cell nevi showing "activity" during pregnancy[10].
3. Nevus-cell nevi which histologically show evidence of "unrest", e.g., precancerous junction nevi.

Treatment Generally Considered Advisable

1. Those closely related conditions with clinical features which suggest possible malignant transformation which is believed to take place in a reasonably high percentage of instances (e.g., melanotic freckle of Hutchinson or circumscribed precancerous melanosis[11]).
2. Benign juvenile melanomas[12].
3. Nevus-cell nevi in subungual areas.

Treatment Controversial

1. Nevus-cell nevi at sites of repeated trauma.
2. Nevus-cell nevi appearing beyond the second decade of life.
3. Nevus-cell nevi located on palms and particularly soles.
4. Nevus-cell nevi on genitalia and mucous membranes.

advocated. More recent figures, however, show that the incidence of pigmented lesions at these sites is closer to 25 per cent[9]. In view, then, of the frequency with which pigmented nevi appear on palms and soles, their removal from our entire population does not seem feasible. Furthermore, based on the comparatively low incidence of malignant melanomas at these sites, the excision of all such pigmented nevi does not seem warranted.

Misconception 3: One should never cut into a nevus, for example, to obtain a biopsy, because it will cause malignant transformation.

In our opinion this, too, is a misconception, for to our knowledge: 1) proof is lacking that cutting, or even traumatizing, a benign nevus-cell nevus has ever produced malignant degeneration; 2) we know of no histologically proven benign nevus-cell nevus which became malignant following biopsy; 3) malignant melanomas remain one of the less common malignant tumors (about 1 per cent) in spite of the fact that thousands upon thousands of nevi have been biopsied or destroyed; and 4) it is a prevalent opinion that malignancy already existed in those nevi for which the therapy administered was held to blame.

Of course, where malignant melanoma is strongly suspected on clinical grounds, diagnostic biopsy should not be performed without careful review of all the circumstances pertaining.

Misconception 4: All pigmented nevi should be removed.

We cannot agree with this precept for the various reasons already stated. The indications for the removal of pigmented nevi (including junction and compound nevus-cell nevi) are few. With the exception of treating them for cosmetic reasons, the indications for therapy are listed in Table I.

Treatment: When the decision has been made to remove a particular nevus, it is then necessary to choose a method which will be not only therapeutically correct but from which a cosmetically acceptable (though not always essential) result can be anticipated.

Junction and compound nevi, with few exceptions, should be surgically excised allowing but 1-2 millimeters of normal tissue at the periphery—in other words, the excision should be a conservative one. The excised specimen should be submitted for histopathologic examination by a pathologist specially qualified in tumors of the skin.

Intradermal nevi may be removed both safely and satisfactorily by a variety of accepted dermatologic procedures. The method will depend on the morphology and location of the lesion. Raised dome-shaped lesions, sessile, polypoid and pedunculated lesions may be cut off at the level of the skin surface with scalpel or scissors; any remaining tissue may be lightly electrodesiccated as required. Dark coarse hairs within a lesion should be removed *first* by electrolysis; sometimes the removal of the hairs alone will result in sufficient shrinking of the nevus to make it cosmetically acceptable.

For details concerning the recognition of these lesions and the various forms of therapy I would refer the reader to appropriate texts and articles on the subject.

Vascular Nevi

Only the three most common types of vascular nevi, that is, strawberry and cavernous hemangiomas and nevus flammeus (portwine mark) will be considered, and then only briefly.

Strawberry hemangiomas are superficial vascular proliferations which cause an elevated pink to red lesion, usually with an irregular

surface. With diascopy these soft tissues are readily compressible and the blood can usually be expressed from them with ease.

Cavernous hemangiomas occur alone or with a superimposed strawberry lesion. The cavernous elements are usually doughy in consistency and partially compressible and consist of capillaries and larger vessels, together with large vascular sinuses, all of which are located deeper than the vessels of the strawberry hemangiomas, thus imparting to the overlying tissues a bluish rather than red color. Strawberry hemangiomas are commonly found superimposed on cavernous lesions.

The *nevus flammeus* or "portwine mark" is made up of many telangiectatic vessels located quite superficially in the cutis and sometimes subcutis, thus causing the plaques to appear various shades of red and reddish-blue.

The natural history or clinical course of the majority of strawberry and cavernous hemangiomas is quite characteristic—spontaneous involution is the rule[13] and it usually takes place in the following sequence of events: The lesions are present at birth, or appear shortly thereafter. They then grow for several months, sometimes rapidly; but ordinarily they take from three to six months to reach their final dimensions. This is followed by a period of apparent quiescence when they begin to regress spontaneously. Complete disappearance is usually not achieved until the child is four, five or six years old. The clinical characteristics of lesions undergoing involution are rather typical and consist primarily of a lessening of the reddish color and an increase in the bluish tinge; the solid color is broken up by mottled grayish areas which represent the sites from which the vascular elements are disappearing; the tense, shiny surface becomes dull and wrinkles appear. These changes most frequently take place in the center of the lesion and then later involve the periphery. The resulting scar will depend on the original size and extent of the hemangioma and whether the involution was entirely spontaneous or followed ulceration of the surface of the lesion. In general, the final appearance of the residual scar is cosmetically and functionally more acceptable following spontaneous involution than following therapeutic intervention with solid carbon dioxide or, at times, the various other forms of therapy. Sufficient numbers of these hemangiomas have now been observed for spontaneous involution by various authors to substantiate the value of patience and avoidance of therapy in order to obtain the best cosmetic result. There are exceptions to this rule, however, as indicated below.

Many misconceptions regarding the management of vascular nevi exist. Only a few will be mentioned:

Misconception 1: All cavernous and strawberry hemangiomas disappear spontaneously; therefore, they do not require treatment.

As just stated, the majority of strawberry and cavernous hemangiomas do not require therapy because they can be expected to disappear spontaneously; there are, however, certain of these vascular tumors for which attention is necessary. These include: 1) rapidly enlarging hemangiomas; 2) hemangiomas encroaching on external orifices or vital organs; 3) hemangiomas involving wide spread areas; and 4) mucosal hemangiomas.

When the decision is made not to treat a hemangioma, the physician should explain to the parents the ordinary natural course of the majority of such lesions, pointing out, however, that therapy may become necessary. Parents and physician alike should be on the lookout for any unexpected changes, such as sudden enlargement, bleeding, ulceration, infection, necrosis, and interference with or destruction of adjacent vital structures. The patient, therefore, should be seen at regular intervals in order to re-examine the nevus and begin therapy if indicated.

Misconception 2: All strawberry and cavernous hemangiomas should be treated.

There are distinctly two schools of thought regarding the management of these tumors. Those who favor therapy argue that, because of the unpredictable course of hemangiomas, every lesion should be treated while it is still small, or as soon as it comes to medical attention, in order to prevent additional growth. Those, on the other hand, who advocate watchful waiting without treatment, do so by posing the questions, how many typical strawberry and cavernous hemangiomas are seen in adults? (Certainly very few indeed.) And how many unsightly scars or other sequellae are to be seen at the sites of spontaneous involution of these lesions? (Again, very, very few.)

And so the question whether to treat these nevi or leave them alone remains a constant challenge to the practicing physician, for it is *he* who is plagued by parents, grandparents, and other relatives to do something about "that unsightly growth". This is a responsibility that the physician should not take lightly. Should he subscribe to the teachings of the school which favors watchful waiting, as I do (unless there are distinct indications for therapy), he should have the opportunity to re-

examine the lesion at appropriate intervals, and each time should ask the following questions of himself[1]:

1. Does the hemangioma have an atypical appearance, or has its course of growth and involution been other than the usual one?

2. What permanent cosmetic defects may result without therapy, and how important will these defects be? Will therapy improve the chances for a better cosmetic result?

3. What impairment of function may there be or may there develop, if the hemangioma is left untreated (e.g., lesions of palms, soles, genitalia)?

4. What can therapy of the lesion be expected to accomplish that leaving it alone will not do? In other words, what would be the advantages of therapy?

Should therapy become indicated, the characteristics of the lesion, its location, size, depth, rate of growth, and all associated factors should be considered carefully in order to select the appropriate modality. Whatever method is decided upon should be used prudently and with full consideration, not only of therapeutic success or failure, but of the resulting cosmetic appearance.

Of the methods used for treating strawberry and cavernous hemangiomas, x-rays, radium, cryotherapy and the injection of sclerosing substances are the most frequently employed. While there may be specific indications for selecting one modality in preference to another, more often than not a particular method is chosen because it is the one best known to the physician, and/or the one with which he has had the most experience and in which he has the most confidence.

In general, we favor ionizing radiation when therapy is definitely indicated, provided it is given in sub-erythema doses and then only according to a schedule which allows for very slow involution of the nevus. In this way, where nature is given "a boost", so to speak, the cosmetic result is likely to simulate that achieved through spontaneous involution and the radiation dose remains well within limits of safety.

Because of the very superficial location of some of the smaller strawberry hemangiomas, solid carbon dioxide may sometimes be used to advantage. Treatment with this form of cryotherapy may be repeated every few weeks, with caution being taken not to produce excessive ulceration and a subsequent undesirable scar. Because of the superficiality of the freezing produced by carbon dioxide, this form of cryotherapy is of no value in the treatment of cavernous hemangiomas.

In addition, various sclerosing agents, as well as various surgical techniques, have been used successfully in the management of selected strawberry and cavernous hemangiomas.

Most important, therapy should be administered carefully and conservatively, for we have all seen the undesirable and unhappy results achieved through too vigorous cryotherapy, excessive doses of radiation and a haphazard injection of sclerosing substances. Even with surgical extirpation, recurrences have been known.

Misconception 3: There is no effective therapy for nevus flammeus.

With the knowledge that these lesions seldom fade appreciably and rarely disappear completely spontaneously, all too commonly the parent is told that nothing can be done for a child's birthmark when it is the ordinary, garden-variety portwine stain. Actually, there are three approaches which may be used:

1. The topical application of thorium X, a radioactive material which has been used in dermatologic practice for over 45 years without producing harmful sequellae. Treatments are given once every six weeks for as many as 10, 20 or more times[14]. In our experience, and that of others, about one third of the patients treated in this manner show considerable and satisfactory lightening of the lesion, another one third show but little improvement and the remaining one third show no response whatsoever.

2. Cosmetic camouflage. Certain of these lesions may be satisfactorily covered by special make-up preparations, such as pancake, "Spotstik", and "Covermark" (Lydia O'Leary).

3. Also reported to be of value is the Conway technique of tattooing insoluble pigments into the cutis and subcutis above the vessels, thus hiding the lesion[15].

The proper management of these vascular nevi can be achieved only if the physician is familiar with their natural course, the complications which may occur, the various forms of therapy with their indications and contraindications, the therapeutic results that may be anticipated and the sequellae which may follow. He must be prepared to handle the unexpected emergencies and should seek consultative advice whenever needed.

For details concerning the diagnosis and therapy of these vascular nevi, here again, I must refer the reader to comprehensive texts and specific articles on the subject.

Summary and Conclusion

I shall conclude this very condensed presentation of a most important and broad subject by pointing out that 1) there is no substitute for experience in making the clinical diagnosis of pigmented lesions of the skin; 2) the therapy of nevus-cell nevi and hemangiomas must be selected to meet the needs of the particular situation, and lastly, 3) in the management of skin lesions the therapeutic modality should be carefully chosen so as to achieve not only a rapid and permanent cure but, whenever possible, one that will be cosmetically and functionally acceptable.

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PSYCHOANALYSIS 1959*

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NINETEEN HUNDRED AND FIFTY-NINE is a celebrant year in the history of psychoanalysis. It is the 50-year anniversary of 1909, and 1909 was critical for Freud and for psychoanalysis. This was the year when Freud, on invitation from Stanley Hall, visited America and lectured at Clark University. This was the year that saw the birth of the first international psychoanalytic publication—the *Jahrbuch für Psychoanalytische und Psychopathologische Forschungen*, with Bleuler and Freud as *Herausgeber*, and Jung as Editor. This was the break-through year which, according to Jones, marks the beginning of the international recognition of psychoanalysis.

Fifty years is a goodly span of time, one that lends the right perspective for the evaluation of historic, and notably intellectual, eventuations. Fifty years allows for the overlapping coexistence of three generations. Ortéga y Gasset[1], in his *Man and Crisis*, makes much of this. And indeed it is a profound insight. "The present", Ortéga wrote, "is rich in three great vital dimensions which dwell together in it, whether they will or no, linked with one another, and perforce, because they are different, in essential hostility one to the other. For some, 'today' is the state of being 20, for others 40, and for still another group, 60; and this, the fact that three such very different ways of life have the same 'today', creates the dynamic drama, the conflict, and the collision which form the background of historic material and of all modern living together".

I take it, our concern is with the historic background of psychoanalytic thought and development. In these relations we need recognize that ours is the generation of "twenty", to whom Freud stands as of the "sixty", and Brill, Jones, Ferenczi, and Jung, as the generation of "forty". Those who come after us will have a different linkage. It will

* Presented at a meeting of the American Society of Psychoanalytic Physicians, at The New York Academy of Medicine, December 3, 1959.

no longer be possible for them, or their descendants, to have known "the men who had known the man". Their vision, and I fear too, their understanding, while possibly more penetrating and expansive than ours, will lack that element of authenticity which is vouchsafed only to him "who was there when it happened". All of which is prelude to the affirmation that it is not only desirable that we should evaluate psychoanalysis in 1959, but that it is our obligation, our debt-to-be-paid, to those who by the accidents of later birth, will not be able to know of these matters save only by hearsay. But how is one to assess Freud's psychoanalysis? It would seem most reasonable to review in brief the major postulations of psychoanalysis, to take note of those which experience and further study have validated, to catalogue those which in contrast have not survived close scrutiny and clinical trial, to see where the embrace of psychoanalytic thought has extended to other fields and disciplines, and conversely, how and to what extent psychoanalysis has been affected by concurrent developments in science and philosophy.

Confessedly, this is a most challenging and pretentious perspective, one that cannot be fulfilled in the limitations of an essay. Still, it may yet be useful to sketch the terrain, even if we cannot or may not fill in every detail.

I think it were wrong not to begin our evaluative venture with a full appreciation of the historic significance of Freud and his psychoanalysis. We must, as good historians, differentiate between the historic significance of an event, a personality, or an idea, and its ultimate, scientific validity or moral value. No one can deny great historic significance to Napoleon, though many will doubt his moral worth. Copernicus is historically no less a revolutionary thinker because his astronomical calculations have been proved wrong, i.e., inadequate. The impact of Darwin's teachings on evolution have had an historic effect on thought which is unaffected and independent of the questions raised on the correctness of his theoretical premises.

In that historical perspective, Freud and his psychoanalysis stand forth as preeminent in the dimensions of greatness, as do Karl Marx and his *Das Kapital*, and Charles Darwin and his *Descent of Man*. Freud, and those to whom he is compared, gave a new turn to the thinking of mankind.

Freud challenged the 19th century faith in man as a rational animal. This was a faith nurtured for some 300 years, and seemingly brought to

a fine point of iridescent perfection just about the time (in the final decades of the 19th century) when Freud came forth to challenge it.

Nineteenth Century rationalism was *strictly* rationalistic, i.e., logically positivistic. It failed to perceive and could not recognize the rational function of the irrational. That is what Freud underscored, not precisely in this formulation, not with this implied selfconsciousness, but by indirection, in a piecemeal, clinical, empirical manner.

It were difficult to overestimate the significance, the import for human thought and destiny of the Freudian challenge. It is equally difficult to grasp its full weightiness, its fertility, its explosive potentials. Only the authoritarian states, the Communists, for example, appear to have some grasp of the transcending significance and the overwhelming surcharge of psychoanalytic premises and hypotheses. To them, Freud and psychoanalysis are anathema: an infamous adversary to be excoriated. *Ecrasez l'infame*. The rest of the world, including also some of the psychiatric and the psychoanalytic portion, have, I would venture the opinion, only a vague and none-too-secure appreciation of the overriding significance, and the immutable validity of the essential premise of psychoanalysis. There are, of course, some exceptions among the psychiatric group, and for them this ventured opinion does not hold. But the group is not large. The rest are too easily made anxious by the advent of every new therapeutic modality offered for the treatment of psychiatric symptomatology. Many behave as if they feared that some new drug or combination of drugs would rob them of their specialty. They hasten, lest they be left behind, to get on the latest in the therapeutic caravan of bandwagons.

All of this is sad to behold, and yet it cannot but enhance our appreciation of the magnitude and significance of Freud's premise—the affirmation of the transrational nature of man.

Freud's psychology has been described as an "instinct psychology". The term "instinct" is currently in ill repute, and for very good reasons. For to the instincts have been credited all orders of motivations and behavior, from the belief in a personal God, to the loving graces of maternity. Call them instincts or not: Freud was cognizant that *before reason there was life*, and that life was impelled and regulated, and *is so even now*, by certain indwelling forces, not to be distinguished from life itself, which in a measure embrace, but most generally transcend that which the human mind recognizes as rational. Freud perceived, too,

that the rational, and with it the moral and the social, often impedes the free play of the primal forces and drives of the living process, that their effective reconciliation fosters the rational, the moral, and the social, but that when left unreconciled, that is, in abiding conflict, ill health, in the physical as well as in the experiential and behavioral spheres, may, and commonly does, result. This, according to Freud, was the genesis of the neurosis. The neurosis, be it noted, need not be entirely absorbed in the overt pathology reflected in variant behavior, but may also turn upon the innate vital forces, that is, the primal drives. This is dramatically represented in anorexia nervosa, and more reconditely in certain forms of schizophrenia.

This most significant element of Freud's psychoanalysis, that which I would deem the most revolutionary and the most fundamental component of his system of thought, has not been effectively challenged in the past 50 years. On the contrary, it has been confirmed, validated, reenforced, and elaborated in many ways, and in numerous proximate and remote disciplines–in social anthropology, in animal psychology, in ethology–to name but a very few of the disciplines.

It is not possible to elaborate on this affirmation–time does not allow it. It is, however, desirable to define the essential quality of this "significant element in Freud's psychoanalysis". It amounts to the following: *Freud signalled the existence and the effective operation of a science of relations, as distinguished from the science of things.* How else could one account for the cure of an hysterical paralysis, since the count of things involved remains unchanged both before and after? It matters not that this science of relations had been known and understood in time past, and had been forgotten, or overlooked. It came as a revitalizing breath when it was advanced anew by Freud. Affirming this, I am aware that I seemingly credit Freud with more philosophical preoccupation and sophistication than is historically warranted. Freud was not interested in philosophy and conceivably, had he been confronted with the above formulation, he would have disclaimed it entirely. But that is of little matter; what one does may have little bearing on what one initially intended, and the effects yielded may not be cognizable to the one who effected them. Pavlov, in demonstrating the possibility of inducing experimental neurosis, little thought, nor later recognized, how much he thereby gave support to Freud's theory on the genesis of the neurosis. Pavlov never did recognize this, and yet that does not alter the fact.

Here I must round off this portion of my presentation, intended to attest to the historic significance and greatness of Freud and psychoanalysis. I have dwelt upon this at some length because I wanted to set down not only the acknowledgment of Freud's significance and greatness, but also more particularly wherein these dimensions of his significance reside. Many acknowledge that Freud is a most preeminent character in recent history. Not as many, however, know precisely how and why. Among the many literati and philosophers who have undertaken to treat of the greatness of Freud, only Isiah Bowman has impressed me as fully knowledgeable. Of course I do not know them all, and some, I confess, I have read with a jaundiced eye. Yet the reason I am concerned with literati and philosophers is that the challenge voiced by Freud in the realm of psychiatry is one we face in every realm of being. How that challenge is met, how it will be resolved, will deeply influence the coming destinies of man.

From the basic premise of psychoanalysis we now need turn to some of its derivative formulations, bearing in mind that our concern is with how they have "stood up" in the intervening years, i.e., from the time of their formulation to the present. Without doubt the Freudian concept of the Unconscious is crucial to both psychoanalytic etiology and psychoanalytic therapeusis. The Unconscious is posited as the realm of the repressed, whence it, the repressed, can be evoked into the Conscious by the exercise of free association. Repression is effected by the Censor, whose repressive operations are overcome, in the therapeutic situation, by the permissiveness of the atmosphere, and I would add, the evocative support of the therapist. No matter how "passive" the analyst may be, he still does insist that the patient withhold nothing and speak out everything that comes to mind. This evocation of the repressed from the Unconscious into the Conscious finds ultimate justification and presumed warrant in the postulation that the neurosis is fundamentally the resultant of repressed "material", material which will not stay repressed, but rather issues forth to embarrass the operations of the Ego and personality in devious and seemingly inexplicable ways. We see then that the major theoretical components involved in these operations are the Unconscious, the Censor, recall by free association, and the cathartic and curative effects of the recall.

Before treating of these theoretical components, it is desirable to observe that Freud linked all of them in what can only be described as

a closed system. This was, according to Freud, the basic pathodynamic pattern of the neurosis. It likewise was *the* rationale for analytic therapy by free association.

In evaluating Freud's postulates concerning the Unconscious, *et al.*, one must therefore bear in mind not merely their individual validity and significance, but also that of their postulated interaction: thus it is quite possible that each postulate has its singular validity and yet, collectively, they may fail to add up to Freud's hypothetical summation. This, to anticipate somewhat, is characteristic of the greater part of pristine analytical theory. It is seldom entirely wrong or in error, but it is likewise not as correct, as inclusive, as broadly valid as it is pretended or claimed to be. Thus, to restate and to amplify this affirmation, there can be no doubt that the nonconscious is functionally a massive, and probably the largest, component of the operational human psyche. The Unconscious in the Freudian sense is unquestionably a component of that nebulous terrain, the nonconscious. Where it is functionally located, at the core or at the perimeter, and how close it lies to the realm of the conscious, are still unresolved questions. But of the existence of the Freudian Unconscious there can be no question, nor of the fact that its dynamic content is provided by repression, nominally exercised by the Censor. All this can incontestably be demonstrated experimentally in the phenomenon of posthypnotic suggestion. However, acknowledging the existence of, and the dynamic potentials of, repressed "material", contained in the Unconscious, does not by any warrant commit one to the acceptance of Freud's contention that *repression* is the sovereign cause of the neurosis. In fact, it isn't, and probably is less so today than it was in the time of Freud. The neuroses have many etiologies, and *repression* in the Freudian sense is only one among them, and rarely so in the pure and dominant form.

In this crucial reality, and in the fact that Freud was too much possessed with his own ideas to welcome or to adsorb into his metapsychological system those of his associates, particularly when they were divergent from his own, lies the explanation for the emergence of so many "splinter" schools of psychoanalysis. Unquestionably some of the splintering resulted largely from the stresses of conflicting ambitions, nurtured by proud personalities. But even in the absence of pride and ambition, it could not but become clear to the experienced and the studious that Freud's theories on psychopathology and psychotherapy were

far too narrow in their derivations and too restricted in their perspective on life's experiences, to illuminate the entire field of the psychoneuroses. Many among Freud's early associates ventured to ask if other dynamic combinations besides repression, and other crucial segments of experience besides sexuality, might not be involved in the engenderment of the neuroses? Those who pressed their inquiries too far, too persistently, and too vigorously, found themselves sooner or later outside the psychoanalytic pale, disparaged, discredited, and denied. I am sure I need not read you the impressive roll of the Freudian dissidents. What I would rather note here, for I've never seen it treated, is the problem of those who were early drawn to Freud and to analysis, whose names are listed as having shared in the nascent stages of analysis, but of whom one hears little thereafter; who seemed to have vanished early and noiselessly. How many among these, I wonder, were also dissidents, unknown, because they did not choose to fight? And I wonder, too, how great, in consequence, was the loss for psychoanalysis. In these connections I recall the paper presented by Professor J. J. Putnam of Harvard, at the third International Psychoanalytic Congress, meeting at Weimar, in 1911. The title of his paper in German was "*Ueber die Bedeutung philosophischer Anschauungen and Ausbildung für die Entwicklung der psycho-analytischen Bewegung*" (On the significance of philosophical ideas and training for the development of the psychoanalytic movement). The burden of this exposition was a protest and warning against the monolithic theorizing and circular thinking that was patent in psychoanalysis. "Psychoanalysis", Putnam wrote, "is and should be recognized as being an instrument, not a doctrine. It binds us to no particular faith; it does not prevent us from holding any conviction as to universal truths. I doubt, however", Putnam continued, "whether psychoanalysis gives us all we need"[2]. I am also moved to cite Sandor Ferenczi as the outstanding example of one who, having grown in experience and being natively studious, could not but perceive, and react against, the narrow and rigid formulations of Freudian theory and practice. Ferenczi did not merely protest—he experimented. He explored new theoretical formulations, and new procedures in therapy. Had he lived longer there is little doubt that he, too, would have "broken" with Freud, or more likely, would have been "disowned".

It is neither possible, in the time available, nor do I believe it would be profitable, to review here the distinctive academic and practical

elements propounded and advanced by the factional schools of analysis. I would rather attempt to describe what seems to me to be their common accent. It is, I would say, an accent on the *extrapersonal*, in contradistinction to the *intrapersonal* factors, both in etiology and in therapy. This affirmation may at first sound a bit cryptic and, paradoxically, also too simple. Definitely, it requires explanation and elaboration. This I will attempt forthwith. Freud's theoretical formulations are concerned almost entirely with the intrapersonal operations and relations of the individual's psychic mechanism. Specifically, Freud's formulations revolve about the historic interrelations of the Id, Ego, and Superego—these interrelations being reflected in the individual's competences, adequate or otherwise, to deal with the reality about him. The psychoneuroses, according to Freud, were primarily the resultant of intrapsychic, or intrapersonal, conflict. The resolution of such conflict, according to Freud, would relieve the sufferer of his neurosis. This was uniquely the individual's task—to be worked out and achieved intrapsychically, that is, intrapersonally. The psychoneurotic individual could thus be said to carry *within himself entire* both the cause and the cure of his psychoneurotic disorder.

But it was not long before it became clear, to some, that conflict, with its consequent repression, was not the sole, nor even the most important etiological factor in the psychoneurosis. Far more common were the factors of deprivation, and these derived most frequently from certain dimensions of the extrapersonal realm.

Allow me to paraphrase this in the form of a pat sentence. It became evident that "one's psychic being depended not only on how one reacted to *what* happened, but also on *that* which happened or *didn't happen!* Frequently that which should have, but didn't happen was the more important part of experience: hence the term 'deprivation' ".

This should be a concept easy to grasp. But it proved almost inconceivable to the generations who thought of disease only in terms of specific noxious agents. They could not conceive that the absence of a something essential to the economy of the being could also be the cause of disease. In fact, even in clinical medicine, this was not clearly demonstrated before 1912. In that year Casimir Funk, who the year before had coined the word "vitamine" (*sic*), showed that beriberi could be dramatically cured (and also prevented) by the administration of a crystalline derivative from rice polishings. This established the existence

of what F. Gowland Hopkins of Cambridge, England, termed "disease with a minus sign".

In psychiatry, "disease with a minus sign" was not so clearly conceptualized nor so conclusively demonstrated as it was in clinical medicine. What did issue was the recognition that the psychological mechanism and man's psychic functions were deeply influenced by the individual's milieu-experiences, by his physical, economic, and cultural environment, by that which can be termed the "extrapersonal factors". As a result, some of Freud's associates and followers turned to the study of issues and matters beyond the Unconscious, the Censor, and repression. In accord with the common nature of historical developments, all this took place, not with conscious intent, but gropingly. The picture I have drawn is retrospective, it was not anticipated before it eventuated.

The interesting feature of this development is that different personages in the psychoanalytic realm chose to explore and to develop different segments of the milieu realm: Adler, the socio-somatic; Jung, the archaic-cultural; Wilhelm Reich and Franz Alexander, the immediacies of the external world and their constrictive influences. There were others who became involved in other pursuits, for the field of the extrapersonal is enormous indeed. One of the very earliest of the analytic deviants was Trigant Burrows, who dug into the basic psychologic consequents of the stereotypy of social organization and social communication. Burrows articulated some of the questions currently asked in existential-analysis: whether society itself is not one of the most significant pathogens in the realm of the psychic, impeding by its "socially sanctioned illusions" any essentially correct comprehension by the individual of his own actual being. Normal society, Burrows maintained, presents socially the same dissociations and image substitutions as are presented in the neurotic personality. "Normal social structure", he argued, "is not basic or fundamental in nature but, on the contrary, represents a secondary and substitutive fabric which, like the fabrications of the neurotic, is without direct biological or organic foundations"[3]. Burrows was not a nihilist, nor an anarchist, nor antisocial. On the contrary, he envisaged a higher order of social relatedness, more consonant with man's essential, biological being. Burrows had few followers, and appeared to have made no impression at all on the psychoanalytic movement. Jones, in his biography of Freud, hardly notices him, and does not even honor him with one of those mordant sentences

with which he spikes his comments on the other dissidents.

Better known, more widely recognized, and of deeper immediate effect, were the dissidents Karen Horney and Harry Stack Sullivan, both of whom gave rise to independent schools. Common to their separate orientations is this, that both Horney and Sullivan extended the theoretical encompassment of Freud's psychoanalysis to include the individual's contiguous *real* world, and also, those other mortals in it that impinge upon his own being. I have used the expression "to extend the encompassment of Freud's psychoanalysis". I must add that this is not intended to imply an initial total acceptance of Freud's formulations. On the contrary, much was discarded, sloughed off; only the core was retained and added to. But herein lies the difference between two orders of Freudian dissidents. One group sought to displace Freud's theories with their own "monolithic formulae". Among such I would count Adler, Rank, and Reich. The other group, including Jung, Ferenczi, Horney, Sullivan, Alexander, and Schilder did not seek to displace but to build upon, to extend the encompassment of Freud's psychoanalysis. In the end the results are at times hardly identifiable with the original, but if I may compound my figures of speech—"the foundations of large structures most often lie hidden".

I have thus far said but little about psychoanalytic therapy, concerning myself almost entirely with psychoanalytic theory. But, of course, theoretical changes must perforce be reflected in therapeutic practices. On occasions they precede theory. In "classical psychoanalysis" (the phrase is Ferenczi's), free association, including dream analysis, was the sovereign therapeutic means. It accorded very well with Freud's fundamental hypothesis that it was the repressed "material", resident in the Unconscious, that was animating the neurosis. In free association, and in dream analysis, the repressed material was likely to emerge into consciousness, for in both free association and in dreams the repressing censor is, to an effective extent, evaded. But, when the postulated etiology came into question, the therapy, too, could not but be questioned. And such indeed was the case, notably first with Rank and Ferenczi. Ferenczi is the more significant of the two. Ferenczi was one of the first to break into the traditional passivity of the analyst's role. He was not unwilling to confront his patient with blunt inquiries that called for deliberate responses, rather than a roaming over the Unconscious. Nor was he loath to, or hesitant in, proffering to the shy, anxious,

or distressed patient, assurance, encouragement and affection. Ferenczi advocated, not a superficial and hasty, but rather an active analysis. He also recognized that many patients bring with them not merely a history of conflict, but also of deprivation, "that the origin of neuroses was to be found in definite traumas, particularly the unkindness or cruelty of parents. This had to be remedied by the analyst's showing more affection toward his patient than Freud thought proper or necessary"[4].

What was rather falteringly initiated by Ferenczi, who was ever loath to confront or deny Freud in anything, and did so only in pain and under duress, has been the consistent pattern of change in psychoanalytic therapy. This is perhaps best mirrored in Franz Alexander's therapeutic procedures[5] as well as in those developed by Frieda Fromm-Reichmann[6]. The once rigid requisites and the paraphernalia of "classical analysis" (Ferenczi's phrase) now have historical significance rather than current pertinence. Glover[7], in his confidential study of the practices of British psychoanalysts, all of them members of the Institute, reveals "much unorthodoxy among the orthodox".

In all respects, and for the majority of psychoanalytically trained and oriented psychiatrists, there has been an adaptive loosening of therapeutic procedure—away from doctrinaire rigidity toward an objective effort to meet the multiphased challenge of the therapeutic problems and the patient's needs. Anamnestic depth is not sacrificed, but is attained more directly with a greater economy in time and effort. Insight, and its application to past and current experience, is favored by the analyst's more active participation in the therapeutic process. More effective, more courageous use is made of the transference-countertransference situation and relationship. The current reality problems of the patient are, when it is profitable or necessary to do so, accepted as legitimate therapeutic items and used as leverage for uncovering the past, as well as for the achieving of a clearer understanding which the patient may gain by ventilating them. The therapeutic relationship is not as exclusively confined to analyst and analysand, as it formerly was, but may now, to varying degrees, be extended to embrace other persons intimately and significantly impinging on the patient's being. Not a few analysts are now "treating" both marriage partners, and will see, in analysis, or contiguously, child and parent, and/or siblings.

Of course there are some who will insist "All this is not analysis". But such a protest cannot be taken in earnest; and with such protestants

it is profitless to discuss the issue. Of them it needs be said, in Virgil's words to Dante,

Non ragionam di loro
Ma guarda e passa.

I come to the end of my review of "Psychoanalysis in 1959" with a sharp sense of frustration. So much that belongs within the scope of such a review is left untouched. So many points of issue remain undefined and unsettled. But that cannot be helped, for even if the requisite knowledge and scholarship *were* available, time, for certain, is not. This much, however, I trust has been made clear in this review: the grandeur of Freud's genius, and the revolutionary challenge of his analytical psychology; the expanding comprehension of the intrapsychic dynamics of the individual, and their, in part, derivative relation to the ecological setting in which the individual has his being.

Freud was, in the Oslerian categories, an innovator, that is, of the highest order among the medical greats. He will be remembered, as is Paracelsus, long after his "system" has been overlaid by the increments in knowledge and insight that are the burden of time. For, if there be aught that we who are the heirs of Freud are bound in the debit to our inheritance to comprehend, it is that we and all of mankind are currently in the adolescence of cultural development. Before us, in the person of our descendants, lies the prospect of a glorious adulthood, when mankind will culturally come of age. When that eventuates, Freud will be recalled and honored as one among the very few of whom it can truly be said—he was a *Wegweiser*.

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NEW YORK PATHOLOGICAL SOCIETY

ABSTRACTS OF PAPERS AND DISCUSSION

Presented at the Meeting on December 10, 1959, at The New York Academy of Medicine

Immunologic Mechanisms in Experimental Vasculitis

FRANK J. DIXON

University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania

This presentation deals with several experimental models in which immunologic reactions are associated with vasculitis. The models chosen have readily identifiable antigen-antibody reactions and may be analogous to some human diseases.

In serum sickness, the essential immunologic event is the interaction between circulating antigen and newly formed antibody, initially in an environment of antigen excess, and finally in one of antibody excess. Coincident with the antigen-antibody reaction are inflammatory and necrotizing changes in small and medium-sized arteries, particularly of the heart, and an endothelial proliferation in the glomerular capillaries. Fluorescent antibody observations reveal the presence of antigen and probably antibody in these vascular lesions.

The essential immunologic feature of the Arthus reaction is the interaction of antigen with antibody in the walls of small vessels. One of the reactants must be in the circulation and the other injected locally to insure the immunologic reaction within the vessel wall. Fluorescent antibody studies reveal a sub-endothelial antigen-antibody deposit in small vessels in the Arthus site. In the absence of circulating polymorphonuclear leukocytes, this antigen-antibody deposit appears to elicit little or no inflammatory reaction. In the presence of polymorphonuclear leukocytes, the polys infiltrate the affected vessels and phagocytize the antigen-antibody complexes, which they then catabolize and/or carry off. Thus, this phlogogenic stimulus, initiated by antibody-antigen interaction, is fully expressed only in the presence of polymorphonuclear leukocytes.

A chronic glomerulonephritis, morphologically and clinically quite similar to its human counterpart, can be produced in rabbits by daily intravenous injections of foreign serum proteins. This course of antigen injections results in a prolonged antigen-antibody interaction in the circulation. Glomerulonephritis develops in those rabbits which produce some but not enough antibody to combine completely with and cause the elimination of all circulating antigen. These relatively poor antibody producers have a continual antigen-antibody reaction occurring in the circulation in an antigen-excess environment. Fluorescent antibody studies indicate the heavy deposition of antigen and probably antibody along the basement membranes of affected glomeruli. Electron microscopic observations reveal these antigen-antibody deposits to be in contact with the outer surface of the basement membrane, between the membrane and the epithelial cell cytoplasm. Similar electron-dense deposits have been observed in human chronic glomerulonephritis.

Studies on Transplantation Immunity

CHANDLER A. STETSON, JR.

Department of Pathology, New York University-Bellevue Medical Center

and

EMMERIK JENSEN

University of Copenhagen, Denmark

The role of circulating antibody in the rejection of homografts is still not generally recognized, in spite of the growing number of reports of the existence of cytotoxic antibodies in the serum of grafted animals and of the passive transfer of anti-graft immunity by such serum. Much of the argument against the participation of serum antibodies is based on early work with cell-impenetrable chambers which indicated that host cells, but not antibodies, are involved in graft destruction. More recent work has indicated that grafts in such chambers can indeed be destroyed by antibody in the absence of host cells. While immunity to grafts of dissociated normal or malignant cell suspensions has been readily transferred with serum, such has not usually been the case with orthotopic homografts (of skin, for example). Preliminary evidence has been obtained that in such vascularized grafts there exists a blood-graft barrier to the passage of antibodies, and that graft destruction may be accomplished by cytotoxic antibodies only after some increased permeability of blood vessels is produced, perhaps by a local delayed hypersensitivity reaction.

DISCUSSION

JOHN G. KIDD: The concepts and phenomena of immunology have in the past given rise to much food for thought and to many problems of interest for pathologists. We have heard this evening from two investigators who are now working effectively in this field. Their papers show clearly, it seems to me, that newer techniques of immunology, when industriously applied to problems having to do with alterations in tissues and cells *in vivo*, can still disclose findings having at once wide biological implications and special interest and importance for those who are interested in the causation and nature of disease.

Dr. Dixon and his group are to be congratulated upon their mastery of the fluorescent antibody technique—first developed by Coons and Kaplan—and for their critical application of this technique and other immunological procedures to the study of experimental vasculitis and glomerulonephritis. With respect to the nature of the induced arteritis, it seems to me that they have in this lesion a very close experimental model of the acute stages of naturally occurring periarteritis nodosa—though this disease has intruded itself somewhat less often upon our thoughts during the past several years than it used to do some years ago when the American public was consuming several hundred tons of sulfonamides per annum. Furthermore, the reversible glomerulonephritis associated with induced serum sickness, shown in Dr. Dixon's first group of slides, although clearly unlike the lesion of chronic progressive glomerulonephritis that we see at the postmortem table, may still provide something of a counterpart for the lesion of naturally occurring acute glomerulonephritis, for it is well known that most patients who develop this disease recover from it in due course.

By means of the fluorescent antibody and

other immunologic techniques in combination with light and electron microscopy, Dr. Dixon has shown quite precisely the localization of antigen and antibody—presumably joined together in the form of complexes—at the sites of injury in these induced acute lesions. His findings bear upon the causation and pathogenesis of several experimental diseases and their naturally occurring phototypes.

In his more recent studies, as illustrated in his second group of slides, Dr. Dixon has produced a progressive chronic glomerulonephritis which, to my eye at least, has all the earmarks of chronic active (Type I) glomerulonephritis as we see it in human beings. I question whether he would have achieved this noteworthy result had he not been at once an experienced pathologist with facilities for work on an extensive scale, and at the same time a competent immunologist with due regard for the values of quantitation. For, as you will recall, when he gave bovine albumin repeatedly over long periods of time to rabbits that were good antibody producers, and thus stimulated with relatively little antigen the formation of very large quantities of antibody, the lesion did not develop; and the same was true when he gave the antigen in excessive amounts to animals that were unresponsive or poor producers of antibody. The chronic nephritis developed only in those rabbits in which complexes composed of more or less equivalent amounts of antigen and antibody were presumably present in the circulating blood during considerable periods of time. I am sure we shall all await with interest the publication of these findings in detail, and their inevitable extension in numerous directions.

Now Dr. Dixon has not travelled all the way from Pittsburgh merely to hear nice things said of his work. He expects, I am sure, at least one captious remark, and I am prepared to deliver this. But first I wish to commend him further for not using the term "collagen disease" in his presentation this evening. It seems to me high time that pathologists generally—at least those who have regard for precision in terminology and nomenclature[1]—should again follow Dr. Klemperer's lead[2] and re-examine the basis upon which they have employed this term during the past several years. Recent observations on the nature of disseminated lupus, including those of Dr. Klemperer, lead us away from the notion that collagen is primarily injured in this disease[3]. Furthermore, the observations of George Murphy indicate that heart muscle, not collagen, is primarily injured in rheumatic disease[4], and the observations of other workers provide more than an indication that what has so long and glibly been called fibrinoid is, in large part at least, merely fibrin[5, 6]. In this latter relation I recall the extraordinary reserve that Dr. Klemperer has always displayed toward the terms "fibrinoid degeneration" and "fibrinoid necrosis"; he has been at once vigorous, articulate, and logical in pointing out that these terms lack specificity and precise meaning[3]. And this leads me to my captious comment: Twice this evening, within earshot of us all, Dr. Dixon has pointed to "fibrinoid" in his acute lesions. I hope that others will not conclude from Dr. Dixon's reference to fibrinoid that collagen is primarily injured in the lesions he has produced; also that Dr. Dixon can manage in due course to define precisely the point of injury.

Dr. Stetson has concerned himself mainly with the mechanisms whereby mammalian organisms react against transplanted tissue cells and bring about their death. As he has pointed out, this is a problem that has interested many investigators during the past 50 years. It is also a problem having quite wide implications—bearing, for example, upon the nature of genes and of antigens, upon the phenomena of hypersensitivity, and, more remotely perhaps, on the manifestations of auto-immune states. Furthermore, during the past 20 years there has been a renewal of interest in this problem; and from recent work in this field a new and fundamental phenomenon—namely, *immunological tolerance*—has come as a by-product.

My own interest in this problem has centered around immunity to transplanted cancer cells. Much of the early work in this field was done with these as materials. Some 50 years ago, when cancer began to be studied intensively in laboratories all

over the world, only random-bred mammals were available, and investigators who then undertook to transplant a spontaneous tumor in this species found it necessary to use dozens of hosts in order to get a take in one or a few animals, and they were able to keep the tumor going only by using large numbers of hosts during several serial transfers. Even after this critical period, many of the grafts grew only briefly and then regressed, the implanted hosts being immune thereafter. Now it has become known to everyone that genetically determined antigens, present in cells of the graft but absent from tissues of the host, stimulate in the host a specific immune reaction which somehow overcomes the graft. Yet the nature of the immune reaction and the mechanism whereby the grafts are overcome have remained uncertain to the present day; much controversy still centers around the question whether humoral antibodies or "immune" lymphocytes effect the result, as Dr. Stetson has told us.

Such knowledge as we now have of immunity against transplanted tissues has not by any means burst suddenly upon us. Many years ago, Dr. Rous showed that immunity against transplanted cancer cells can be induced artificially by injecting either living cancer cells or living embryonic (non-neoplastic) cells into alien hosts, the immunity thus induced being effective against grafted normal tissues as well as against grafted neoplastic tissues[7]. Dr. William Woglom, who used to come often to the meetings of this Society, wrote two detailed reviews on immunity to transplanted cancer cells, one published in 1913 and the other in 1929. In the latter publication, which deals with observations recorded in more than 600 papers, Woglom noted particularly that all attempts theretofore to demonstrate humoral antibodies as responsible for immunity to transplanted cancer cells had failed, and he concluded that a "generalized host resistance" of unique sort was probably responsible when tumor cells were overcome in alien hosts[8]. Some years later, upon reviewing the work of Lumsden and the earlier work of Gorer on isoantibodies in relation to immunity to transplanted cancer cells, I concluded that the isoantibodies that they had found in the blood of resistant hosts might well prove to be epiphenomena in relationship to the regression of transplanted tumors[9]. More recent work makes it plain that the effects of isoantibodies in this relationship remain still uncertain[10, 11]. By contrast, Da Fano[12] and J. B. Murphy[13] long ago convinced themselves that lymphocytes are probably responsible for the regression of grafted tumors in resistant and immune hosts.

And this brings me to the contentious aspect of what I have to say about Dr. Stetson's presentation. Some years ago, after inbred animals had become readily available, Dr. Toolan and I, with Dr. Ellis participating in a part of the work, made a histologic study of regressing C3H mammary carcinomas in Strain A mice—this with the aim of learning, if we could, the means whereby cancer cells are overcome in alien hosts[14]. We found that cells from a C3H mammary carcinoma, implanted into the subcutaneous tissues of animals of that inbred strain, began to proliferate within 24 to 36 hours following implantation and continued to do so thereafter until death of the host, without calling forth any inflammatory response or being influenced in any discernible way by immunological factors. When we put these cells into albino (Strain A) mice, we found that they also grew during the first five days following implantation, and precisely as in C3H mice. Quite regularly on the fifth or sixth day, however, lymphocytes began to appear about the growths in the alien Strain A mice. The lymphocytes soon became numerous, and they promptly began to infiltrate the small nodules of proliferating tumor cells from the periphery inwards. As the lymphocytes established intimate contact with the proliferating tumor cells, the latter began to die one by one, the process proceeding quite rapidly until the last tumor cell had died, usually before the 12th day. Furthermore, as they died, the tumor cells exhibited an interesting sequence of cytologic changes which was wholly unlike that to be seen in tumor cells dying from other causes—e.g., as the result of anoxia, or when heated. When a Strain A mouse had overcome its first C3H tumor and was later reimplanted, the lymphocytes accumulated

much more promptly. Within 24 hours they began to collect in considerable numbers about the implanted lymphoma cells, and within 48 to 72 hours the lymphocytes were not only exceedingly numerous but also closely approximated to the proliferating tumor cells. Soon the latter began to exhibit the distinctive cytologic changes, and within five or six days following implantation they were all dead[14]. In further experiments we procured blood serum and suspensions of lymph node cells from immune Strain A mice, often from animals that had been repeatedly reimplanted. The serum had no effect on the tumor cells *in vitro*, whereas suspensions of cells from the lymph nodes always acted powerfully against them. Hence my own experience has led me to the conclusion[14]—previously reached by Da Fano[12] and by Murphy[13] and subsequently arrived at by Mitchison[15] and by Weaver, Algire and Prehn[16]—that "immune" or "sensitized" lymphocytes probably overcome tumor cells when these are transplanted to resistant hosts[18]. It was inevitable that we should see a parallel between these observations and those of Landsteiner and Chase, which indicate that cells are responsible for certain of the manifestations of hypersensitivity[17, 18].

In spite of my own experience in this relation, it seems to me wholly appropriate that Dr. Stetson should question the conclusion that lymphocytes bring about regression of tissues transplanted in alien hosts, and that he should mobilize from his own experiments and from the observations of others such evidence as he can find to support the inference that humoral antibodies are responsible. For after all, to paraphrase a saying of Josh Billings: a difference of opinion can lead to experimentation, and perhaps, indeed—to discovery. Surely, in a field as complicated as this one is, the repetition of work and the application of differing points of view are much to be desired if the points at issue are to be resolved.

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OCTOBER 24 to 28, 1960

FRONTIERS IN MEDICINE AND SURGERY — 1960

PANEL MEETING — 4:30 P.M.

Monday October 24

RECOGNITION AND MANAGEMENT OF COMMON VIRAL DISEASES

Moderator: YALE KNEELAND, JR., M.D., *College of Physicians and Surgeons, Columbia University*

LECTURES — 8 P.M.

GENETIC DISEASES

G. W. BEADLE, Ph.D., *California Institute of Technology*

GENETICAL VARIATIONS IN THE SERUM PROTEINS OF MAN

ALEXANDER G. BEARN, M.D., *The Rockefeller Institute*

PANEL MEETING — 4:30 P.M.

Tuesday October 25

ARTERIAL OBSTRUCTION IN THE EXTREMITIES: MEDICAL AND SURGICAL ASPECTS

Moderator: JERE W. LORD, JR., M.D., *New York University Post-Graduate Medical School*

LECTURES — 8 P.M.

CLINICAL IMPLICATIONS OF CYANOSIS

HARRY W. FRITTS, JR., M.D., *New York University College of Medicine*

PRESENT UNDERSTANDING OF THE ROLE OF GLIADIN IN THE STEATORRHEA SYNDROMES

CHARLES D. MAY, M.D., *College of Physicians and Surgeons, Columbia University*

PANEL MEETING — 4:30 P.M.

Wednesday October 26

"AUTO-ANTIBODIES" AND DISEASE

Moderator: HENRY G. KUNKEL, M.D., *The Rockefeller Institute*

LECTURES — 8 P.M.

CURRENT STATUS OF BONE MARROW TRANSPLANTATION

J. W. FERREBEE, M.D., *College of Physicians and Surgeons, Columbia University*

LECTURES — 8 P.M. (continued)

Wednesday October 26 *(continued)*

CURRENT STATUS OF BONE TRANSPLANTATION
CAPTAIN G. W. HYATT, MC, USN, *U. S. Naval Medical College*

CURRENT STATUS OF KIDNEY TRANSPLANTATION
JOSEPH E. MURRAY, M.D., *Harvard Medical School*

PANEL MEETING — 4:30 P.M.

Thursday October 27

THE VALUE OF ANTIBACTERIAL PROPHYLAXIS IN MEDICAL AND SURGICAL PROCEDURES
Moderator: WALSH McDERMOTT, M.D., *Cornell University Medical College*

LECTURES — 8 P.M.

MUSCULAR DISEASE
DAVID GROB, M.D., *State University of New York, Downstate Medical Center*

PYELONEPHRITIS
EDWARD A. GALL, M.D., *University of Cincinnati College of Medicine*

PANEL MEETING — 4:30 P.M.

Friday October 28

RECOGNITION AND MANAGEMENT OF THE COMMON PSYCHONEUROSES
Moderator: DANA W. ATCHLEY, M.D., *College of Physicians and Surgeons, Columbia University*

LECTURES — 8 P.M.

NUTRITION AND THE BRAIN
RAYMOND D. ADAMS, M.D., *Harvard Medical School*

SURGICAL ASPECTS OF INTERNAL CAROTID OBSTRUCTION
MICHAEL E. DeBAKEY, M.D., *Baylor University College of Medicine*

NEUROLOGICAL ASPECTS OF INTERNAL CAROTID OBSTRUCTION
H. HOUSTON MERRITT, M.D., *College of Physicians and Surgeons, Columbia University*

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A buffet supper will be served each evening in the Presidents' Gallery at $3.75 per person. It is felt this will add to the pleasure of the interlude between the afternoon and evening sessions. *Advance Reservation and Check* (payable to The New York Academy of Medicine) must be received no later than Monday, October 17, 1960.

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George A. Perera, Quentin B. Deming

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**Berberian, D. A., and Slighter, R. G.: J.A.M.A.* 168:2257 *(Dec. 27) 1958.*

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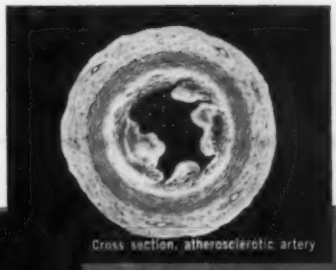

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*Knudsen, E. T., and Rolinson, G. N.: Lancet 2:1105 (Dec. 19) 1959.

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1. Research Laboratories, Mead Johnson & Company, unpublished data, available on request. 2. Holt, L. E., Jr., and McIntosh, R.: Holt Pediatrics, ed. 12, New York, Appleton-Century Crofts, Inc., 1953, p. 224.

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